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Table of Contents.

Listerian Oration.[1]

THE CHEMOTHERAPY OF PNEUMOCOCCAL INFECTIONS.

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"Et causæ quoque estimatio sæpe morbum solvit."—Celsus, Liber I.

THE invitation to deliver the Listerian Oration confers an honour of which the recipient must necessarily be profoundly conscious: a distinction rightly regarded as a pinnacle of achievement in the medical profession of this country.

In a period of unrest such as now afflicts the world, when ethical values tend to be submerged in a tide of physical violence and the rule of law and order is challenged by force and brutality, a consideration of the nobler works of man in the service of the sick and disabled is an opportune reminder of the part played by the healing art in the evolution of our civilization, as opposed to the forces causing destruction of human life.

Only too often in the history of the world has the malign influence of scientific men whose genius has been devoted to devising engines of death, appeared to counterbalance that of their colleagues whose efforts are directed towards the preservation of life.

There is much to commend the institution of an annual memorial lecture as a means of keeping fresh among us the memory of our departed masters. It ensures that each year one person at least, the chosen lecturer, shall give some thought to the life and work of the great man under whose auspices he is to speak in the attempt to recapture the intellectual mood of his day, to appreciate the nature of the problems which then confronted the thinker and to estimate the measure of success which was achieved in their solution. (Lord Macmillan: "Law and Other Things".)

[1] Delivered at a meeting of the South Australian Branch of the British Medical Association on May 30, 1940.

The influence of Lister and his teachings is so universally recognized that any attempt to evaluate the effect of his work upon modern medicine and surgery should be entirely superfluous to an audience of professional men. Moreover, "there is", as Osler said, "surely no doubt that the leaven of science working in the individual leavens in some degree the whole social fabric".

Educated as we have been in an atmosphere of surgical asepsis, it is sometimes difficult to realize that until the Listerian era the problem of wound infection was an unsolved mystery, which had confronted mankind since the beginning of time. Although in civil practice the principle of aseptic surgery has almost removed the risks of infection in deliberately planned surgical procedures, the wounds resulting from war injury provide a field for the application of the antiseptic principle in wound infection as originally taught by Lister, and the importance of the prevention of extraneous infection by antiseptic methods becomes again of paramount importance in military surgery. It would be well indeed if the army surgeon were to reread Lister's "Collected Papers", which would be found to contain most, if not all, of the knowledge essential for the treatment of war wounds at the present day.

The modern concept of the bacterial origin of infective processes has in large measure evolved from the work of Lister in his enunciation of the antiseptic principle, correlated as it was with the genius of Pasteur in demonstrating the nature of fermentative processes and the growth of bacteria. From these foundations have been built the modern science of bacteriology and the recognition of the infective agents in disease, with ever-increasing knowledge of the means of prevention and treatment.

For the human race it is fortunate indeed that men of genius gifted with the inquiring mind have arisen continuously to keep alight the lamp of learning and further the aims of medical research, for, although discovery in the medical sciences has at times appeared to be of the nature of happy accident, it is well to remember the dictum of Pasteur:

In the field of observation chance favours only the mind that is prepared.

In the words of Moxon ("Pilocereus Senilis and Other Papers"):

> A golden thread has run throughout the history of the world consecutive and continuous, the work of the best men in successive ages.

Study of the ætiological agents in disease has indeed been progressive and continuous, and has led up from the morass of ignorance towards the safe ground of rational therapy.

The recent evolution of chemotherapy in acute infection may therefore be regarded not inappropriately as a sequence of the work of the master whose life we commemorate.

Modern Chemotherapy in Pneumococcal Infection.

It is my purpose to place before you some aspects of the treatment of acute infective disease, particularly pneumonia, employing the methods of modern chemotherapy. Pneumonia, so long ranking high among lethal illnesses, is by these means now rapidly becoming adequately controlled.

When it was my privilege two years ago to deliver the E. C. Stirling Lectures in this city, attention was drawn to the relative inadequacy which existed in Australia in the treatment of the pneumonic diseases. In the short period of time which has elapsed, this situation has undergone remarkable change. In May, 1938, the National Health and Medical Research Council of the Commonwealth provided a grant to enable an adequate survey to be made of the ætiological agents causing the pneumonic diseases in the State of New South Wales. Further assistance has since been provided from the same source for the systematic investigation of the modern treatment by chemotherapy under controlled conditions in a large metropolitan hospital.

Although these investigations are still incomplete and official publication of results has not yet been made, it is permissible, in view of the general interest and present importance of the subject, to indicate the nature of the work which has been carried out in relation to the incidence of pneumococci in cases of acute respiratory infection in this country, and to review the results so far attained by chemotherapy, correlating the findings in this comparatively limited series with published results from world-wide sources.

Type Incidence of Pneumococci in Acute Respiratory Infection.

In the course of the investigation carried out at the Kanematsu Memorial Institute of Pathology at Sydney Hospital, specimens of sputum from 1,000 consecutive patients with acute infection of the lower portion of the respiratory tract have been examined, with the object of determining the presence of pneumococci and establishing the incidence of the various types of this organism. Pneumococci have been recovered from 754 specimens (Table I). Reference to these figures indicates that the predominating types of pneumococci in this series have been I, III, IV, V, VII and VIII, which accounted for more than 50% of pneumococci recovered. Comparison with standard figures from other parts of the world indicates *inter alia* that there is a striking difference in the incidence of Type II infections in the local series. This observation may be of considerable importance when comparisons are being made of the mortality figures for pneumonia in this country and elsewhere, because Type II infections, infrequent in this series, are recognized as being particularly lethal in other countries. On the other hand, Types III and VIII, which are of relatively virulent nature, constitute 22% of the total local strains, contrasted with 11% in an American series. It should be remembered, however, that very large numbers are necessary to minimize statistical error in an investigation of this nature. Moreover, the specimens examined were derived chiefly from the city of Sydney and surrounding districts, and may not prove to be representative of the country as a whole. It is also not improbable that the type incidence of the various infective agents may be variable in different years. With the advent of efficient chemotherapy the determination of the individual type of pneumococcus present has become of less importance than formerly, when serum of the specific type was the most effective means of treatment.

TABLE I.

Results of Examination of Specimens from 1,000 Cases of Acute Respiratory Infection at the Kanematsu Memorial Institute of Pathology, Sydney Hospital, from March 8, 1938, to April 30, 1940; Pneumococci were recovered in 754 Specimens (75·4%).

Type.[1]	Total.	Approximate Percentage.
I	139	18·0
II	5	Less than 1
III	69	9·0
IV	56	7·0
V	51	7·0
VI	22	3·0
VII	82	10·0
VIII	101	13·0
IX	15	2·0
X	19	2·5
XI	5	Less than 1
XII	28	3·7
XIII	22	3·0
XIV	8	1·0
XV	14	1·8
XVI	5	Less than 1
XVII	11	1·4
XVIII	9	1·0
XIX	7	Less than 1
XX	29	3·8
XXI	7	Less than 1
XXII	18	2·5
XXIII	3	Less than 1
XXIV	1	Less than 1
XXVII	2	Less than 1
XXVIII	6	Less than 1
XXIX	2	Less than 1
XXXI	6	Less than 1
XXXII	4	Less than 1
Untyped to date	8	
Total	754	

[1] Types I, II, IV, V, VII and VIII accounted for over 50% of the pneumococci recovered.

The essential aim in the investigation of acute respiratory infections has now become the determination of the incidence of a pneumococcus as the causal agent in the varied kinds of respiratory diseases. Identification of the type of pneumococcus should still form part of the routine investigation of respiratory infections, even although it has been shown that sulphapyridine is efficient against pneumococci generally, including certain types—for example, III and VIII—formerly thought to be relatively resistant to treatment. The trend of recent work appears to indicate that resistance to chemotherapy may be a peculiarity of certain strains of the organism rather than an attribute of particular types of pneumococci. Moreover, it has not yet been finally determined whether the best results, especially in bacteriæmic cases, may not demand a combination of serum and chemotherapy. As far as this country is concerned, the almost prohibitive cost of serum has led to the employment of chemotherapy practically exclusively, although representations made to the Federal Government were effective in having the duty removed from imported pneumococcal serum as from January 28, 1939.

Pneumococci in Secondary Pneumonia.

It is interesting to note that in a recent American review of the incidence of pneumococcal infections it has been authoritatively estimated that 85% of primary pneumonic diseases of adults and at least 54% of the pneumonias of childhood are attributable to pneumococcal infection. It should also be remembered that secondary pneumonic processes associated with acute infective diseases (measles, pertussis *et cetera*) are frequently of pneumococcal origin.

With the advent of efficient chemotherapy it therefore becomes more than ever necessary to concentrate attention upon the nature of the infective agent in respiratory disease, rather than to endeavour to distinguish too closely between the variations in the pathological changes produced in the organs affected (lobar pneumonia or bronchopneumonia, pleurisy, bronchiolitis *et cetera*). This observation is of particular importance in view of the fact that deaths attributed to bronchopneumonia and to

unspecified pneumonia exceed those recorded as due to lobar pneumonia in the State of New South Wales.

The importance of the whole problem becomes obvious when the actual number of deaths from pneumonia is reviewed. Statistics from the Department of Health of the State of New South Wales indicate that in the seven-year period from 1932 to 1938 inclusive, the average number of patients *per annum* whose death was attributed to lobar pneumonia was 664. The average annual number of deaths from all other forms of pneumonia (broncho-pneumonia and pneumonia unspecified) was 930 (Figure I).

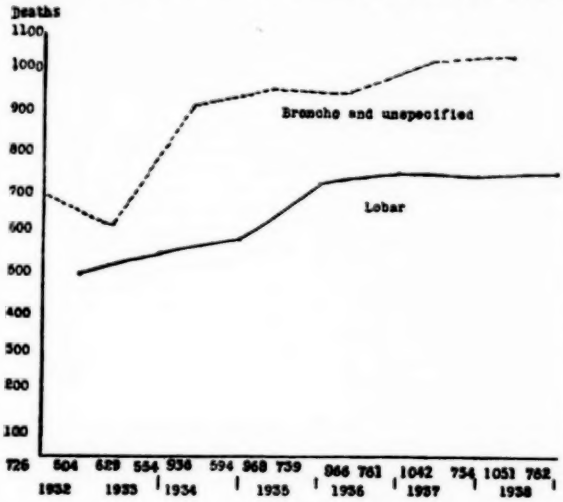

FIGURE I.

Annual deaths from pneumonia in New South Wales.

From these figures it will at once be apparent that the effective control of the pneumonic diseases is a matter of vital importance to the country. The significance of efficient chemotherapy in these diseases can be fully appreciated only when sufficient time has elapsed to produce adequate statistical records over a long period; but it is already apparent from data obtained in other parts of the world that the death rate from these diseases has been greatly diminished. It has been authoritatively estimated that a general average mortality rate in pneumococcal pneumonia of approximately 27% has been reduced to 8% or less.

A review of published statistics of lobar pneumonia treated with sulphapyridine may now be considered. In a record of world statistics quoted by H. L. Marriott in *The British Medical Journal* of November 11, 1939, it is shown that of 1,991 treated cases there was an average mortality rate of 5·5%. In a series of 63 cases of pneumococcal infection recorded at the Sydney Hospital since the present investigation was commenced, eight deaths have occurred from various causes (Table II). A detailed analysis of these fatal cases has been made. Three patients of the series had grave disease apart from pneumonia (lysol poisoning, tuberculosis, infective endocarditis) and are therefore excluded from the statistical record relating to frank pneumonia. In the 60 cases remaining there were five deaths, a mortality rate of approximately 8%. This figure appears to be in general accord with the world's figures for unselected cases including all age groups.

Method of Investigation and Treatment.

The method adopted for the investigation and treatment of the patients recorded in this series has been standardized in order that adequate comparison might be made with the results of other workers.

The principle of treatment employed had as its objective the early arrest of the disease by producing a rapid and effective concentration of sulphapyridine in the blood by administration of a relatively large initial dose of the drug (four to six grammes), followed by doses of one gramme every four hours until fever had been completely controlled for forty-eight hours. From this point onwards the dose was reduced to one gramme three times a day, or in other instances to 0·5 gramme every four hours. It was considered desirable, following accepted principles, to aim at regular administration at intervals of four hours whenever practicable, continuing treatment for a period of five days normally. The total quantity of sulphapyridine administered to each patient was of the order of 20 to 25 grammes, the effects being regularly controlled by daily estimation of the concentration of free sulphapyridine in serum, by leucocyte counts and by careful clinical observation. The normal response to efficient therapy in early cases of lobar pneumonia has come to be regarded as rapid defervescence, with cessation of toxæmic symptoms in twenty-four to thirty-six hours, followed by uncomplicated convalescence. Complete defervescence occurred within forty-eight hours in 45 of the 60 cases. In six instances the fever appeared to be unaffected by the administration of sulphapyridine.

The case-recording system has been designed to establish clearly the initial symptoms of acute respiratory infection, the degree of lung involvement, the nature of the infecting agent, the response to standardized treatment by sulphapyridine, and the estimation of the concentration of the drug produced in the blood serum. Careful observation has been made of the occurrence of cyanosis or of other toxic symptoms attributable to the drug.

In common with the experience of other observers, it has been found that suspension of the drug prematurely because of the production of nausea or for similar reasons was undesirable, in that freedom from complications was thereby not ensured, and that if there was a recurrence of fever a second favourable response to further administration was frequently not obtained.

In explanation of these findings it has been suggested that a power of sulphapyridine resistance has been acquired by the invading organism. This phenomenon appears to be exhibited in a case in which severe toxic symptoms associated with cutaneous eruptions followed the second course of administration.

It is generally held that nausea as an isolated manifestation of susceptibility to the drug should not be regarded as a reason for withholding it; rather, that efforts to maintain adequate concentration should be continued by parenteral administration if necessary. When patients exhibit this peculiarity the administration of the drug powdered and suspended in milk or in some other bland fluid or with the addition of an alkaline powder has been employed to overcome the difficulty. The most recent reports indicate that freshly prepared mucilage of acacia (half the strength of the preparation given in the British Pharmacopœia) is the most suitable medium; four grammes of mucilage are allowed for each gramme of sulphapyridine. In exceptional instances only has it been necessary to resort to intramuscular or intravenous injection of the soluble sodium preparations. Nicotinic acid in doses of 50 milligrammes has proved of some value in lessening toxic symptoms.

TABLE II.

Pneumonia Treated by Sulphapyridine. Sydney Hospital Series.

Number of Patients.	Number Afebrile in 24 Hours.	Number whose Fever was Uncontrolled.	Average Maximum Serum Concentration per 100 Cubic Centimetres.	Number who Recovered.	Number who Died.	Mortality Rate.
60	45	6	7·5 milligrammes	55	5	8·3%

The administration of large quantities of bland fluid is considered desirable to replace fluid lost and to render less likely the occurrence of renal complications due to the deposition of crystals of acetylated sulphapyridine in the urinary tract and to minimize toxic effects generally; the daily fluid intake should be of the order of 3,000 to 3,500 cubic centimetres to ensure adequate urinary dilution.

Complications in the Recorded Series.

Complications occurring in the cases discussed have been tabulated (Table III). Nausea, headache and vomiting in varying degree have been observed in approximately half of the cases. These symptoms can usually be disregarded, being surely a paltry price to pay for freedom from the drudgery of unpalatable mixtures and continual hypodermic punctures previously in vogue. It will be noticed that cyanosis has been recorded in several instances. In all cases this has been due to methæmoglobinæmia and has rapidly disappeared after suspension of the drug.

TABLE III.
Analysis of Complications in 60 Cases.

Complication.	Number of Cases.
Delayed resolution	12
Pulmonary œdema	5
Pleural effusion	4
Empyema	2
Peripheral circulatory failure	7
Distension (marked)	5
Delirium	11
Cyanosis	16
Skin rashes	2
Hæmaturia	1
Photophobia	1
Blurred vision	1
Dizziness	1

Skin rashes have been relatively infrequent. In the case figured as illustrating failure of response following a second course of intensive treatment, a morbilliform rash followed by urticaria with the formation of serous blebs and subsequent desquamation was observed. This patient was not in the hospital series, and the normal check of sulphapyridine concentration and leucocyte count was not carried out.

Delayed resolution has been recorded when pronounced physical signs of lung involvement have persisted for a period of three weeks or longer. It appears to be a matter of common experience that whereas in normal cases the toxic and febrile manifestations of the disease are readily controlled by sulphapyridine, the pathological processes of pneumonia, once established in the lung, seem to go through the classical phases of consolidation and resolution, little if at all hastened by the apparent arrest of the bacterial invasion. When patients are treated at a very early stage of the disease, when the infection is presumably bacteriæmic and the changes in the lung have not passed beyond the initial phase of congestion, it appears that in some instances the pathological process is arrested. These findings have been based on repeated clinical observations supported by serial radiological investigations. Serous pleural effusions, which underwent gradual resorption, have been recorded in four cases, and may be regarded as abortive empyemata.

The infrequency of suppurative complications observed (two cases) is in keeping with the experience of other observers, which tends to indicate that the incidence of empyema and lung abscess has been decreased, although it is commonly held that the drug appears to be inactive in producing effect when pus has formed in a closed cavity. The explanation has recently been offered tentatively that in such instances the sulphapyridine is inactivated as a bacteriostatic agent by the presence of peptone or other products of breaking-down protein. It is important to note that the administration of sulphapyridine does not interfere with the normal formation of antibody in the patient's serum.

Blood Changes.—The white cell count has been carefully observed in view of the possible effects of the drug in producing granulocytopenia. The number of leucocytes in the blood of patients on their admission to hospital has averaged from 10,000 to 20,000 per cubic millimetre; in four cases only was leucopenia recorded. In each of these instances the number of leucocytes rose after treatment. In two cases only did leucopenia appear to follow the administration of the drug, and in each instance the number of leucocytes rose rapidly after its suspension. No blood changes of serious moment have been encountered.

Correlation of Clinical Results with the Concentration of Sulphapyridine in the Serum and Other Body Fluids.

Attempts have been made in this investigation and by various other observers to establish a correlation between the concentration of free sulphapyridine in the blood serum and the effective control of infection.

With the standard dosage employed it has been found that serum concentrations varied within wide limits concurrently with effective clinical control of the disease as evidenced by defervescence and lessening of toxic symptoms. The average concentration produced in the serum after standard dosage has been of the order of 7·5 milligrammes per 100 cubic centimetres; the original concentration reached after twenty-four hours from the commencement of treatment has been maintained throughout the period of intensive administration in 50% of the cases; in other instances suspension or irregularity of dosage for idiosyncrasy or failure of absorption or for other reason has caused variations in the level. Serum concentration is to some extent varied by fluid intake and excretion.

The consensus of world opinion appears to be that a concentration of at least 4·0 to 4·5 milligrammes per 100 cubic centimetres should be aimed at, although almost all clinical observers record that remission of symptoms does not seem necessarily to depend on the attainment of a given concentration. In general toxic manifestations appear to be associated with high concentrations in the serum; in particular instances idiosyncrasy to the drug may be the determining factor. As has previously been suggested, the susceptibility of the organism to chemotherapy may vary according to particular strains rather than according to specific types of pneumococci. Unassessable powers of resistance to disease intrinsic to the individual may determine the issue in some instances. The rate and degree of absorption of the drug are apparently very variable.

In a case of severe infection by pneumococcus Type VIII effective control was achieved after normally adequate doses had produced a serum concentration of less than one milligramme per 100 cubic centimetres, whereas in other instances, particularly when there have been associated complications, a concentration of 13·5 milligrammes or more has failed to produce a normal effect.

In a case of pneumococcal meningitis it was found that a concentration of five milligrammes was reached in the cerebro-spinal fluid. In the eighth of the fatal cases (bilateral Type IV pneumonia with multiple lung abscesses) a concentration of 12 to 17 milligrammes per 100 cubic centimetres was recorded in the pleural fluid and 5 to 11 milligrammes in the pericardial effusion.

Limitations of Chemotherapy.

As is inevitable after the introduction of a new therapeutic agent of proven value, a wave of uncontrolled enthusiasm for the newer chemotherapy tends to sweep the profession off its feet. Sound judgement is necessary in the employment of sulphanilamide and its derivatives as in every form of therapy, lest misguided enthusiasm should lead to an ill-advised application of a valuable therapeutic agent. Already the tendency has become manifest to employ these substances indiscriminately for almost every infective process; this has taken the place of careful consideration of the indications for the exhibition of a remedy of extraordinary potency in defined types of disease.

It should be remembered that toxic effects may be produced in cases unsuitable for intensive chemotherapy, particularly when administration is unduly prolonged

without careful control, and that discredit may thus be brought upon an advance in therapeutic methods which rightly ranks in importance with the application of the organic arsenical compounds to the treatment of syphilis and comparable epoch-making discoveries in the field of medicine.

Rightly used, chemotherapy in acute diseases due to infection by pneumococcus, meningococcus, β-hæmolytic streptococcus, *Bacillus coli* and certain other organisms appears to give promise of a gift to medicine almost comparable with the benefit bestowed upon surgery by the antiseptic principle.

The pneumococcus, so long regarded as "captain of the men of death", has in military parlance been "demoted" almost to the rank of corporal in the lethal army. Pneumonia the dread enemy is rapidly becoming a "controlled disease", no longer to take such ruthless toll of human life.

The record of work carried out in the investigations described is by no means complete, having reference as it does to a comparatively small number of cases.

The investigation has been undertaken with the object of recording faithfully the results obtained in the treatment of a series of unselected patients suffering from pneumococcal infection observed under hospital conditions with modern chemotherapeutic methods, under laboratory and radiographic control. An attempt has been made to establish an efficient dose of sulphapyridine to be employed safely in practice, having regard to the concentration of the drug produced by a standard dosage.

The conception of adequate dosage and the value of control by estimations of the serum concentration may become modified as experience widens and observations are made over a longer period of time.

Conclusion.

The subject reviewed is essentially of practical importance to every practitioner of medicine. It is unfortunate that under the conditions of medical service in our community it is but rarely that facility or opportunity comes for an individual to make any appreciable contribution to medical knowledge. It is, however, the duty of hospital units to investigate critically new methods in the treatment of disease under the local conditions of our country, in the hope of adding to the sum of clinical observation and experience.

If this presentation has the effect of stimulating interest in the modern treatment of acute respiratory disease and in the chemotherapy of acute infections generally, encouraging others in the path of clinical investigation, monuments, not unworthy, may arise to honour the memory of Joseph Lister, the master mind in clinical research.

A SUMMARY OF RECENT KNOWLEDGE OF THE CLINICAL APPLICATION AND TOXIC EFFECTS OF SULPHANILAMIDE AND SULPHAPYRIDINE.[1]

By ALEX. MURPHY, M.C., M.B., Ch.M., F.R.A.C.P.,
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THANKS to the untiring efforts of the research chemists, a new era in the chemotherapy of many infections has dawned. However, if full advantage is to be taken of the potentialities of the new products, and if their possible toxic effects are to be minimized, it behoves us to make ourselves familiar with all the available facts concerning their use and abuse.

The number of compounds of what may be designated the sulphanilamide group is growing rapidly, and specific claims are made for each new product as it comes forward; but I propose to confine my remarks tonight to p-aminobenzenesulphonamide and 2-sulphanilamido-pyridine, commonly known as sulphanilamide and sulphapyridine respectively, and possessing the following formulæ and proprietary names (Figure I):

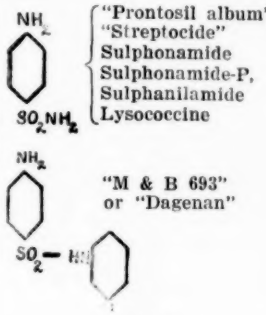

FIGURE I.

In the United States of America and later in Great Britain the proprietary name was to a large extent abandoned, and the latter drug has been called sulphapyridine.

It is of historical interest to note that p-aminobenzenesulphonamide was first synthesized in 1908, but not until Christmas Day, 1932, was the German patent issued for the original "Prontosil" and for several allied products, and the first clinical report of its use appeared the following year.

Absorption and Excretion.

Sulphanilamide.

It has been shown conclusively that after a single dose of sulphanilamide absorption is maximal in from three to four hours, after which the concentration of the drug in the blood drops rapidly, until there is little left at sixteen hours. It is excreted almost entirely in the urine, and therefore if kidney function is depressed normal excretion is inhibited and it accumulates in the body.

An excellent illustration of this fact was furnished by the report of the administration of a single dose to a patient suffering from anuria. Daily estimations showed that the drug remained at an almost constant level in the blood until the onset of diuresis.

It has also been shown to pass readily into the cerebrospinal fluid and into the body exudates and transudates at a level some 10% to 25% lower than in the blood. It passes into the milk of nursing mothers; but the amount taken in by the infant is considered to be too small to have any therapeutic effect, though clinical evidence of toxic manifestations has been reported.

The drug appears in the blood stream in a free and in a conjugated form. In the urine the proportion is about 50% free and 50% conjugated. The conjugation takes place in the liver and provides an example of the detoxicating action of this organ; the process is said to be reversible.

With normal kidney function the administration of large quantities of fluid hastens excretion, while restriction of fluid intake brings about a higher concentration in the blood. The rapid rate of absorption and excretion makes it essential to give the drug at intervals of four hours if a constant level is to be maintained in the blood.

Sulphapyridine.

Sulphapyridine is slower and much more irregular in its absorption; excretion is also much slower, and hence the concentration in the blood is better maintained; but peak concentration is far lower than with a comparable dose of sulphanilamide and varies greatly in different individuals; therefore frequent estimations of the amount of drug in the blood are necessary. It passes into the cerebro-spinal fluid less readily and more slowly than sulphanilamide and does not reach the same concentration.

Dr. Perrin-Long and Dr. Eleanor Bliss, the American authorities on these drugs, sum up the position in the following words:

In comparison with sulphanilamide the absorption, distribution, conjugation and excretion of sulphapyridine is definitely more irregular and capricious; these factors naturally make rational therapy more difficult, because one cannot depend upon the drug reaching the affected tissues in the same manner that one can for sulphanilamide.

Nevertheless the slower rate of excretion provides the explanation of the preference expressed by many practitioners for sulphapyridine, in spite of the fact that it

[1] Read at a meeting of the Queensland Branch of the British Medical Association on March 1, 1940, at Brisbane.

is much more expensive than sulphanilamide. As it is excreted more slowly, the blood level tends to be higher in spite of unskilful administration.

Mode of Action.

In October, 1939, I had the privilege of accompanying Dr. Long to hear an address he gave on the mode of action of these drugs. After dealing in a most interesting manner with his experimental work, and advancing various theories, he naïvely concluded by saying that he did not know how the drugs acted, and that for the time being we had to be content with the simple statement that they inhibited the growth of susceptible microorganisms in the body and *in vitro*.

Diseases in which Sulphanilamide has a Proved Value.

Sulphanilamide is of value in the following conditions:

Hæmolytic streptococcal infections:
(*a*) Septicæmia.
(*b*) Scarlet fever. (It does not influence the acute toxic phase, but reduces complications.)
(*c*) Acute and chronic *otitis media* and mastoiditis.
(*d*) Erysipelas.
(*e*) Puerperal fever.
Meningococcal infections. (Therapy should be intense and a blood level of 15 milligrammes *per centum* should be maintained.)
Gonococcal infections.
Infections of the urinary tract. (It acts in an alkaline medium and is thus effective against urea-splitting organisms, for example, *Bacillus proteus*.)
Brucella infections (undulant fever).
Chancroid.
Clostridium welchii infections (gas gangrene). (It is prophylactic as well as curative; the literature is very insistent on the use of sulphanilamide and not sulphapyridine.)
Trachoma.
Lymphogranuloma inguinale.
Pemphigus.
Subacute bacterial endocarditis.
Infectious mononucleosis (glandular fever). (There have been two recent reports only.)

This preparation is sometimes of value in staphylococcal infections.

My first experience of this was in 1937, when a boy, aged fourteen years, was admitted to one of my beds at the Brisbane Hospital suffering from *Staphylococcus aureus* septicæmia. (Blood culture yielded a growth of *Staphylococcus aureus* in pure culture.) His condition appeared to be hopeless; but intensive therapy, both oral and parenteral, with "Prontosil album" resulted in his recovery.

Method of Administration.

There is little doubt that the administration is carried out far more scientifically and with better results in Canada and the United States of America than in Australia; frequent estimations of the drug concentration in the blood are largely responsible for this. (The laboratory technique is simple, and for the most part is carried out by use of a photoelectric colorimeter.) Here there is a tendency to administer these drugs indiscriminately in almost any infection, and at the same time there exists in the mind of the practitioner a lively fear of toxic effects. Hence in infections in which a definite beneficial effect occurs, the drug is frequently withdrawn as soon as that effect is manifest, and before cure of the infection is achieved.

The point that particularly requires to be stressed is that once therapy is instituted it should be continued until the infection is cured, and not abandoned too early, always provided that no toxic reaction takes place. Age is a factor; young people show a better tolerance than old, and children require a proportionately larger dosage than adults, particularly as restriction of fluid may precipitate acidosis and dehydration in the very young.

Dosage.

In severe infections, in which there may be a fatal outcome, the aim should be to produce rapidly a blood level of between 10 and 15 milligrammes *per centum*. This is achieved by a large initial dose (three to five grammes according to weight and age) and by subsequent four-hourly administrations of 0·5 gramme to 1·0 gramme; the total dose for the first twenty-four hours ranges from two grains per pound of body weight for children to 1·2 grains per pound of body weight for adults. The four-hourly administration is essential on account of the rapid excretion already referred to, and the patient must be awakened if asleep. The four-hourly doses should be continued for seventy-two hours after fever has abated and then maintained at a reduced level until cure is effected.

In milder infections a lower scale of dosage is permissible; four to five grammes may be given in twenty-four hours, a blood concentration of four to eight milligrammes *per centum* being the objective; but again, intervals of four hours must be observed and the therapy must be terminated in the manner mentioned with the higher dosage. On the basis of weight the total amount given in twenty-four hours will range from 1·2 grains per pound of body weight for children to 0·6 grain per pound for adults.

It will be realized that these dosages are the result of averaging, and that unless facilities for estimating blood concentrations are available, the greatest advantage cannot be gained from chemotherapy in each individual patient.

Infections of soft tissues come under the influence of the drug much more rapidly than do those of bone; therefore in the case of the latter results will be slower in their appearance and therapy will have to be maintained for a longer period in order to effect cure.

It must be borne in mind that other well-tried and established therapeutic measures must not be neglected (for example, myringotomy in acute *otitis media*), but employed in conjunction with the drug, with a revised conception of the indications for surgical intervention.

In the case of bacterial endocarditis, in the event of a seemingly favourable outcome, the drug should be administered for weeks after the patient has become afebrile and the blood sterile. It has been my experience that in this disase the fever almost invariably responds to sulphanilamide, but returns to its former level after a period of seven to ten days.

If vomiting or coma prevents oral therapy, parenteral administration of a 1% solution may be employed at intervals of eight hours; but higher dosage must be employed, and oral therapy must be substituted as soon as possible. Give one-half of the total dosage for the first twenty-four hours subcutaneously, dissolved in physiological saline solution, and one-third of the total dose at intervals of eight hours.

The forcing of fluids results in more rapid excretion, while restriction raises the blood concentration. Estimations of the blood level of the drug are therefore essential if this factor is to be accurately judged; but for an adult six pints *per diem* are an approximate optimum amount. Sulphur-containing foods, chief of which are eggs and onions, have been withheld; but in the light of recent work on the ætiology of cyanosis this appears to be unnecessary.

Sodium bicarbonate, three grammes in twenty-four hours, will counteract acidosis and lessen the tendency to nausea and vomiting, and should always be exhibited when parenteral therapy is employed.

Transfusions should be given only if the hæmoglobin value is low or if the donor's blood is known to contain specific antibodies.

Diseases in which Sulphapyridine is of Value.

Sulphapyridine is of proved value in the following conditions: (i) pneumococcal infections, (ii) staphylococcal infections, (iii) gonococcal infections, (iv) meningococcal infections, and (v) subacute bacterial endocarditis (*Streptococcus viridans*).

A greater percentage of this drug is conjugated, and therefore rendered inactive, than is the case with sulphanilamide, and, as already mentioned, absorption is capricious, more so in disease than in health; thus regular estimations of the level in the blood are of even greater importance.

Sulphapyridine is bacteriostatic for all types of pneumococci, and bactericidal for Types I, II, V, VII and VIII at a blood concentration of 10 milligrammes *per centum*.

Worthy of comment is the fact that nausea and vomiting are much more frequent when sulphapyridine is used.

Method of Administration and Dosage.

As soon as a diagnosis of pneumonia is made, the sputum should be examined for the type of pneumococcus present, and if possible a blood culture should be made. Crush the tablets into a powder and give two to three grammes at once, followed by one gramme every four hours for twenty-four hours; then give one gramme every six hours.

If specific serum is available it should be administered, in addition to the drug, to the following patients: (*a*) patients whose blood yields a culture, or who have involvement of more than one lobe; (*b*) patients aged over forty years; (*c*) patients in whom chemotherapy was not commenced within three days of the onset; (*d*) pregnant women and those who contract pneumonia in the puerperium.

Should oral therapy be impossible, the parenteral or intravenous route may be used; but the oral method should be substituted at the earliest possible moment.

Parenteral administration is carried out by the intramuscular injection of "M & B 693 soluble" (one gramme of the sodium salt in three cubic centimetres at intervals of four hours) or by the intravenous injection of the contents of the ampoule made up to 10 cubic centimetres with normal saline solution. Long uses a 5% solution and gives to an adult an initial dose of 3·8 grammes intravenously.

Care must be taken to see that the injection is intramuscular and not subcutaneous, and that none of the solution is placed outside the veins when the intravenous route is employed. The sodium salt is intensely alkaline and may cause necrosis.

Contraindications.

The only real contraindication to the use of either preparation is the knowledge that a severe toxic reaction has taken place on previous administration; yet at times this need not be rigidly adhered to.

Dr. Long informed me that at Johns Hopkins Hospital six patients developed severe agranulocytosis. Of these, one died, and suitable therapy restored the white cell count of the others to normal. Two of the five were then found to have been cured, but in the remaining three the infection for which sulphanilamide had been given persisted and threatened to prove fatal. Administration of the drug was therefore resumed, not without considerable trepidation; but there was no repetition of the fall in the white cell counts, and all patients recovered.

Patients suffering from anæmia, leucopenia and jaundice due to infective agents have all received these drugs, not only without aggravation of these conditions, but with highly beneficial results.

Toxic Effects and their Treatment.

Almost all the known toxic manifestations appear within nine days of the institution of therapy, the exception being agranulocytosis.

Cyanosis.—Cyanosis appears within forty-eight hours and is very rarely due to sulphæmoglobin; thus prohibition of sulphur-containing foods, such as eggs and onions, seems unnecessary. Cyanosis results from methæmoglobin, or from the staining of the red blood cells with an oxidation product of the drug; but it does not seem to affect the oxygen-carrying capacity to an appreciable extent, though it is stated to lower the "flying ceiling" by 5,000 feet. In some of my own early cases spectroscopic examination of the blood by a competent physicist revealed methæmoglobinæmia; this can be prevented or abolished by the administration of one grain of methylene blue three times a day.

Nausea, Vomiting, Weakness and Giddiness.—Nausea, vomiting, weakness and giddiness occur early and are more likely to occur if the patient is ambulatory; but they are rarely severe enough to require withdrawal of the drug, and in the case of sulphanilamide may be abated by the administration of sodium bicarbonate.

Acidosis.—Acidosis is corrected by sodium bicarbonate.

Fever.—Fever is almost invariably the first sign of toxic effect, and the temperature may rise to 106° F. Withdraw the drug and force fluids. Fever may occur as a solitary toxic manifestation, or it may herald the onset of any of the others. The question arises: "How is drug fever to be distinguished?" In infections accompanied by pyrexia adequate dosage should result in a pronounced drop in temperature within three days; if a sharp rise then takes place, in spite of obvious clinical improvement, it is probably due to the drug; a fall in temperature within thirty-six hours of withdrawal of the drug will establish the diagnosis of drug fever.

Convulsions.—Convulsions have occurred after intravenous therapy with fatal results.

Anæmia.—Acute hæmolytic anæmia may occur within three to seven days; stop the administration of the drug, force fluids and give a blood transfusion. Slowly progressive anæmia commences during long-continued treatment; it is not necessary to withdraw the drug if the blood is observed carefully, and transfusions are advisable if the hæmoglobin value drops below 50%.

Agranulocytosis.—Agranulocytosis is the most feared toxic effect and is often fatal; in most reported cases it has arisen after fourteen days. Daily examination of a stained blood film will give warning, and if the neutrophile cells fall below 50%, full white cells counts should be made. As more reports become available, sulphapyridine appears to be more apt to produce agranulocytosis than sulphanilamide. Should agranulocytosis occur, the administration of the drug should be stopped, fluids should be forced, and pentnucieotide, transfusions and intravenous injections of vitamin *C* employed. The formula of nicotinic acid approximates very closely to that of pentnucleotide, and therefore its administration may conceivably be of help. A new drug, adenine sulphate, has been advocated in place of pentnucleotide; but a recent publication suggests that it is less effective than pentnucleotide or sodium nucleinate; however, the number of experiments is admittedly scanty.

Skin Rashes.—Skin rashes of all types have occurred, ranging from morbilliform to urticarial and exfoliative rashes. Photosensitivity has been reported, and patients should avoid sunlight and ultra-violet ray therapy should not be used. Cease administration of the drug and force fluids.

Jaundice.—Jaundice not due to acute hæmolytic anæmia, but to hepatitis, has occurred, but is rare. It carries a high mortality rate. Cease administration of the drug, force fluids, give calcium gluconate intravenously, and a diet rich in carbohydrate.

Neuritis.—Optic and peripheral neuritis are rare, and recovery, which may be slow, takes place after the drug is discontinued. Administration of vitamin *B* may hasten recovery, and rest in bed and support for the muscles are necessary.

Mental Apathy.—Mental apathy and nausea may be countered to a surprising extent by nicotinic acid, 50 milligrammes given three times a day, and all my patients now receive this.

Hæmaturia.—Hæmaturia with decreased renal function may appear during the administration of sulphapyridine. This is due to crystallization of the acetyl salt in the tubules. Cease the administration of the drug and make the urine alkaline.

Conclusion.

It is now recognized that initial inadequate dosage tends to stultify the effect of a subsequent full dosage. The suggestion is that the infecting organism, under these conditions, is able to develop a degree of resistance to the chemical agent. The obvious method of avoiding this is to ensure adequate dosage in the first place, or if the resistant phase has been induced, to employ another member of the sulphanilamide group in subsequent treatment.

It will be appreciated that when these drugs are exhibited it is advisable that the patient should be at rest

and under close medical supervision. Haphazard methods of administration will tend only to bring these most valuable preparations into undeserved disrepute and will expose the patient to greater risk.

In conclusion I wish to state that I have endeavoured to stress broad principles and to avoid tedious detail in the hope that discussion will be stimulated and exchange of personal experience engendered.

SULPHAPYRIDINE IN THE TREATMENT OF PNEUMONIA: A REVIEW OF 80 CASES OF PNEUMOCOCCAL PNEUMONIA.[1]

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DURING last year, when it had become established that sulphapyridine was an effective agent in the treatment of pneumonia, it was decided to conduct a fully controlled investigation of all patients suffering from this disease admitted to Sydney Hospital. The present report embodies the result of this investigation and deals with the response to treatment of all patients with pneumococcal pneumonia, either typical or atypical, over the age of twelve years, admitted to the hospital between July, 1939, and June, 1940.

As soon as the clinical diagnosis of pneumonia was made, sputum was collected for typing and blood was taken for blood culture and for erythrocyte and leucocyte counts. Sulphapyridine therapy was then started immediately. Attempts at blood culture were made every day while the temperature was raised, and daily leucocyte counts and estimations of the sulphapyridine in the blood were made during treatment. The presence of consolidation was confirmed by X-ray examination as soon as possible.

Symptoms, Type Incidence and Mortality Rate.

Eighty patients were treated. Cough and sputum were present in almost every case; pleurisy and rigor were present in approximately 75%, and headache, malaise and vomiting in 50%. A previous history of coryza was present in only 25%, and sore throat was even less common.

The pneumococcus was recovered in 72 cases from the sputum or blood or by post-mortem swabbing. In two cases only was throat swabbing used as a means of obtaining the causative organism. The eight cases in which no typing was done are included, because the clinical history, physical signs and X-ray characteristics all suggested a diagnosis of pneumococcal pneumonia.

Types I, VIII, XII and III appeared most commonly. All patients with Type I pneumonia had a typical onset with a rigor and pleuritic pain, and consolidation was more definitely of lobar distribution than when other types were responsible. All patients with Type VIII pneumonia had a cough for several days or weeks before the onset of consolidation, and in the typical form this type appeared to cause a greater degree of toxæmia than Types I and XII. Type III was particularly culpable in this respect, and also showed a greater tendency to involve more than one lobe. Table I shows the type incidence and the relation of the various types to bacteriæmia, mortality rate and certain complications.

There were nine deaths (11%), three of which occurred within twenty-four hours after admission to hospital. If these are excluded, the mortality rate becomes 8%. All these patients were over the age of fifty years, except one, who was aged forty-seven years. Table II shows the number of patients and the number of deaths occurring in each age group. A short summary of the fatal cases is given in Table III.

[1] This investigation was carried out with the aid of a grant from the National Health and Medical Research Council. The work was supervised by the four senior honorary physicians to the hospital, by the Director of the Kanematsu Institute of Pathology, by Professor K. K. Inglis, by Professor H. K. Ward and by Dr. Marjory Little.

TABLE I.

Type of Pneumococcus.	Number of Cases.	Bacteriæmia.	Deaths.	Delayed Resolution.	Effusion or Empyema.
I ..	9	3	—	2	—
III ..	6	1	3	1	2
IV ..	4	—	1	—	1
V ..	3	—	1	—	—
VI ..	1	—	—	—	—
VII ..	5	—	—	1	—
VIII ..	7	—	—	2	1
IX ..	4	—	—	1	—
X ..	4	—	—	—	—
XII ..	7	2	—	2	—
XIII ..	1	—	—	—	—
XIV ..	2	—	—	—	—
XV ..	5	—	2	—	1
XVII ..	1	—	—	—	—
XX ..	3	—	—	—	—
XXI ..	1	—	—	—	1
XXII ..	2	1	—	—	—
XXVII ..	1	—	—	—	1
XXVIII ..	1	—	—	—	—
XXXII ..	1	—	—	—	—
Pneumococcus untypeable ..	4	—	1	1	1
No pneumococcus ..	8	—	1	3	—
Total cases ..	80	7	9	13	8

TABLE II.

Age Group. (Years.)	Number of Cases.	Number of Deaths.
10 to 19	12	—
20 to 29	10	—
30 to 39	12	—
40 to 49	15	1
50 to 59	21	4
60 to 69	10	4

Treatment with Sulphapyridine.

All patients were treated with sulphapyridine. An initial dose of six grammes was given, followed by a maintenance dose of one gramme every four hours. The administration of sulphapyridine was governed by the following considerations: (i) A high initial dose was considered necessary to cause a rapid rise of the concentration in the blood to the required level. For the purpose of this investigation the optimum concentration was assumed to be between six and ten milligrammes per 100 cubic centimetres. (ii) The concentration of the drug should be maintained at a uniform level throughout treatment. To ensure this, one gramme of sulphapyridine was given every four hours, day and night, until the temperature had been normal for forty-eight hours, and one gramme was given every six hours for a further twenty-four hours. Whenever a dose was missed because the patient was asleep, it was given when he woke or with the next dose. With this scheme of dosage the majority of patients required between 20 and 30 grammes of sulphapyridine; 14 patients received an amount greater than this. If the temperature did not respond within five days it was found that further chemotherapy was ineffective in causing a clinical improvement. (iii) Sulphapyridine therapy was discontinued if such toxic symptoms as rash, leucopenia, anæmia, hæmaturia or uncontrollable vomiting or headache occurred.

Sixty-three patients were given the standard dose. A smaller initial dose was given to the others because of a previous history of renal or hepatic disease or because they had already received sulphapyridine before their admission to hospital. Patients appeared to vary considerably in their ability to absorb and excrete the drug. With the standard scheme of dosage the greatest concentration attained in the blood of individual patients ranged from three to seventeen milligrammes per 100 cubic centimetres. One patient, on account of alcoholic cirrhosis of the liver, was given one gramme of sulphapyridine every four hours, without any initial dose. Within twelve hours he had a blood concentration of 10 milligrammes per 100 cubic centimetres.

TABLE III.

Summary of Nine Fatal Cases.

Patient.	Age. (Years.)	Pneumococcus Type.	Amount of Sulphapyridine Taken. (Grammes.)	Comment.
G.B.	67	XV	6	Took lysol two days before admission to hospital. Died ten hours after admission.
J.H.	47	III	14	Ill seven days before admission to hospital. Signs of consolidation of the lower lobes of both lungs and of effusion on the left side. Post-mortem findings: consolidation of lower lobes of both lungs; left *empyema thoracis*; toxic hepatitis.
C.J.	65	V	6	Ill for an indefinite period before admission to hospital. Suffered from cardiac failure, auricular fibrillation and cachexia. Post-mortem findings: chronic active tuberculous cavity at the apex and lobar pneumonia of the lower lobe of the right lung.
J.B.	50	III	16	Ill three days before admission to hospital. Cardiac failure with auricular fibrillation. Died of acute pulmonary œdema forty-eight hours after admission. Empyema present. Post-mortem findings: consolidation of the middle and lower lobes of the right lung; *empyema thoracis* on the right side.
E.S.	65	No pneumococcus recovered.	19	Ill six days before admission to hospital. Died fifty-two hours after admission. Post-mortem findings: consolidation of the middle and lower lobes of the right lung and of the lower lobe of the left lung.
A.M.	65	IV	16	Cough, sputum and lassitude for seven or eight weeks. Hypertensive cardiac failure. Pulmonary œdema present. Died one week after admission to hospital. Post-mortem findings: hypertensive arteriosclerosis with congestion and œdema of the organs. Consolidation of the lower lobe of the left lung.
J.S.	50	Pneumococcus could not be typed.	35	A week after the temperature came down to normal a pulmonary embolus developed and the patient died. Post-mortem findings: massive pulmonary embolus; no pneumonic consolidation.
W.M.	54	XV	45	Temperature rose again after suspension of sulphapyridine, and consolidation spread. Died in spite of further sulphapyridine. Post-mortem findings: chronic adhesive pericarditis; resolving consolidation in the lower lobe of the left lung.
F.L.	57	III	7	Died within twenty-four hours of admission to hospital. Anæmia. Post-mortem findings: consolidation of the lower lobe of the left lung; hypertensive arteriosclerosis.

Thirty-six (57%) of the 63 patients who received the standard dose maintained a uniform sulphapyridine level in the blood of over four milligrammes per 100 cubic centimetres during the period in which the drug was being given every four hours. The level in the 27 other cases varied considerably; but the majority of the readings were over four milligrammes in 11 cases and under four milligrammes in 16 cases.

No correlation could be obtained between the concentration of sulphapyridine in the blood and the temperature response or the occurrence of delayed resolution.

Toxic Effects of Sulphapyridine.

Toxic effects were observed in 54 cases. Their nature and the frequency of their occurrence are set out in Table IV. Nausea, anorexia and a mild degree of mental depression were common, but no accurate figures were kept of their incidence.

TABLE IV.

The Toxic Effects observed in 80 Patients Treated with Sulphapyridine.

Toxic Effect.	Number of Cases.
Vomiting	35
Cyanosis	23
Headache	11
Rash	2
Anæmia	1
Hæmaturia	1
Photophobia	1

Vomiting was present in nearly 50% of the cases, but was rarely severe enough to necessitate suspension of the drug. Partial alleviation may be obtained if the drug is administered in powdered form in milk or fruit juices, or if a smaller dose is administered more frequently. Most success, however, has been attained by the administration of 50 milligrammes of nicotinic acid with each dose (that is, 300 milligrammes a day).

Cyanosis was observed in all grades of severity. It did not appear to affect the course of the disease, and in no case was sulphapyridine therapy suspended because of its occurrence.

Two patients developed a blotchy, macular, erythematous rash, resembling measles. In both cases this appeared eight days after chemotherapy was instituted.

One patient developed anæmia after receiving large doses of sulphapyridine.

J.W., aged twenty-three years, was admitted to hospital on December 29, 1939, suffering from Type XII pneumococcal lobar pneumonia, affecting the lower lobe of the right lung. A positive culture was obtained from his blood, he was delirious, and he suffered from an extreme degree of peripheral circulatory failure. He had suffered from pneumonia five times in the preceding ten years and had had several operations for nasal catarrh. He was used to drinking one pint of beer a day, and his relatives stated that he was drunk every week-end.

On his admission to hospital the erythrocytes numbered 5,390,000 and the leucocytes 2,640 per cubic millimetre of blood. In spite of treatment he showed little sign of clinical improvement during the first four days. The total number of leucocytes, however, improved progressively until on the third day after his admission to hospital it was 19,520 per

cubic millimetre of blood. On the fifteenth day the hæmatologist, who had been making leucocyte counts every day, reported as follows:

> The sudden appearance of numerous nucleated red cells indicates the necessity for a more detailed blood examination.

A full blood count was made the next day, with the following results. The erythrocytes numbered 1,950,000 and the leucocytes 23,400 per cubic millimetre. The hæmoglobin value was 5·6 grammes per 100 cubic centimetres and the colour index was 1·0. Of the leucocytes, 62% were neutrophile cells, 0·5% were eosinophile cells, 20·5% were lymphocytes, 2·5% were monocytes, 8% were immature band forms, 5% were metamyelocytes, 1·5% were neutrophile myelocytes, and an occasional immature myeloblast was seen. From a stained film it was seen that the hæmoglobin content of the erythrocytes was full. Pronounced anisocytosis, moderate macrocytosis and microcytosis, slight poikilocytosis and pronounced polychromasia were present; numerous normoblasts and erythroblasts were seen.

The following report on the blood count was received:

> There is an anæmia of hyperchromic type with leucocytosis of moderate degree. The most striking feature of the blood film is the presence of numerous nucleated red cells, which range from normoblasts with pyknotic nuclei and hæmoglobinized cytoplasm to normoblasts in which the nuclear structure is less mature and the cytoplasm purplish or light blue in colour. No megaloblasts were seen, but during a prolonged examination an occasional hæmocytoblast (stem cell) was seen.
>
> The blood picture indicates some process involving a rapid destruction of red cells accompanied by a profound stimulation of the bone marrow as signs of active regeneration of both erythrocytes and leucocytes are conspicuous.

After treatment with sulphapyridine was discontinued and iron therapy was instituted, the total number of erythrocytes increased until on February 28, 1940, there were 4,990,000 erythrocytes per cubic millimetre and the hæmoglobin value was 11·4 grammes per 100 cubic centimetres.

In one case hæmaturia developed after the patient had been given 16 grammes of sulphapyridine. There was no history of previous renal disease.

On the patient's admission to hospital his urine gave an acid reaction, had a specific gravity of 1,012, and contained a trace of albumin. There was no macroscopic evidence of blood or pus. On the third day of treatment the patient complained of scalding and frequency of micturition and of pain in the right loin. Examination revealed gross quantities of blood and albumin in an acid urine having a specific gravity of 1,020. Administration of the drug was suspended and large quantities of fluid and an alkaline mixture were given. After two days all traces of blood and albumin had disappeared from the urine and the patient made an uninterrupted recovery.

Photophobia developed in one case soon after sulphapyridine was given, and was relieved by reduction of the dose.

Response to Treatment.

In the large majority of cases a rapid fall in temperature and pulse rate occurred, associated with a decrease in toxæmia and subjective improvement.

In 58 cases (73% of all cases) the temperature had reached normal limits within forty-eight hours of the commencement of treatment. A small rise of temperature after suspension of the drug was found to occur in 12 of these and did not appear to affect convalescence. Five other patients had a rise of temperature which was more pronounced and necessitated the administration of more sulphapyridine.

The relation between bacteriæmia, type incidence and mortality rate is shown in Table I; and it will be seen that Type I pneumococcus appeared to invade the blood stream more readily and with a less degree of toxæmia than other types.

A pneumococcus was obtained in blood culture from seven patients. In each case this was overcome by the administration of sulphapyridine, and further samples of blood taken for incubation in a culture medium were sterile.

No evidence was obtained that sulphapyridine had any effect upon the physical signs or the rapidity of resolution. Further work is needed to determine whether administration of the drug during the congestive phase would prevent consolidation from occurring.

Most patients had, on their admission to hospital, a total leucocyte count of between 10,000 and 20,000 per cubic millimetre. After treatment was commenced there was a gradual return to normal figures, which was usually complete within seven days after the fall in temperature. In a few cases this return to normal was preceded by a temporary rise lasting for one or two days.

The number of leucocytes remained high for longer periods when there was a large area of dense consolidation, and it was therefore considered that a persistently high figure was not an invariable indication of the presence of complications.

Leucocyte counts made on the patient's admission to hospital revealed a figure of below 4,000 per cubic millimetre in four cases. Sulphapyridine was administered and in each case there was an immediate response, as illustrated in Table V.

TABLE V.

The Results of Progressive Daily Leucocyte Counts made during the First Four Days on Four Patients who had Leucopenia when admitted to Hospital.

Case Number.	Number of Leucocytes per Cubic Millimetre.			
	First Day.	Second Day.	Third Day.	Fourth Day.
I	3,060	4,640	7,920	—
II	3,240	—	6,040	7,550
III	3,040	7,960	(Patient died)	—
IV	2,640	6,240	12,740	19,520,

The clinical history of one of these patients is set out in the section on the toxic effects of sulphapyridine.

In only three cases did the number of leucocytes drop below 5,000 per cubic millimetre after sulphapyridine therapy was instituted, and in each case there was a prompt return to normal after suspension of the drug.

Sequelæ and Complications.

The relationship between delayed resolution, pleural effusion and empyema, and the type of pneumococcus is shown in Table I. The incidence of the various sequelæ and complications is set out in Table VI.

TABLE VI.

Complications and their Incidence in 80 Cases of Pneumococcal Pneumonia.

Complication.	Number of Cases.
Delayed resolution (signs still present after 21 days)	13
Delirium	11
Peripheral circulatory failure	8
Distension	6
Pulmonary œdema	6
Congestive cardiac failure	6
Pleural effusion	6
Jaundice	3
Hiccup	3
Meningismus	2
Empyema	2
Otitis media	1
Delirium tremens	1
Pulmonary embolus	1
Femoral thrombosis	1

Pleural effusion was present in six cases. The fluid obtained in four cases was clear and straw-coloured and sterile. In the other two cases the effusions were absorbed without aspiration.

Two patients had a purulent effusion, which was present on their admission to hospital, and both patients died within three days of their admission.

Meningismus was seen in two cases. The signs of meningeal irritation disappeared within twenty-four hours of the patient's admission to hospital, and in neither case was it necessary to perform lumbar puncture.

Summary and Conclusions.

1. Eighty patients suffering from pneumonia were treated, with nine deaths.

2. Pneumococci were recovered in 72 cases. Types I, VIII, XII and III appeared most commonly, and Type III caused the greatest degree of toxæmia.

3. Sulphapyridine was administered to all patients. An initial dose of six grammes was given, followed by a maintenance dose of one gramme every four hours. Patients varied considerably in their power to absorb and excrete the drug; but with this dose 57% of those treated maintained a uniform level of sulphapyridine in the blood of over four milligrammes per 100 cubic centimetres.

4. No correlation could be obtained between the sulphapyridine level in the blood and the clinical response.

5. The administration of sulphapyridine must be continued for the full three days after the temperature has fallen to normal. Even when this was done it was found that a secondary rise of temperature occurred in a few cases.

6. The toxic effects of sulphapyridine therapy are reported.

7. The temperature had reached normal limits within forty-eight hours of the commencement of treatment in 73% of all cases.

8. Leucopenia does not appear to be a contraindication to the institution of sulphapyridine therapy; but its appearance during treatment should be followed by suspension of the drug.

9. The various sequelæ and complications of the disease and the frequency of their occurrence are reported.

Reports of Cases.

ANURIA FOLLOWING TREATMENT WITH "M & B 693".

By T. C. BACKHOUSE, M.B., B.S., D.P.H., D.T.M. and H., F.R.A.C.P.,
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INTERFERENCE with the renal function following medication with "M & B 693" is now a well-recognized phenomenon. It is known to be caused by the deposition in the urinary tract of crystals of an acetylated compound of the drug, but the factors governing such deposition need further elucidation.

Carroll, Shea and Pike[1] have described a case of anuria due to this cause in which cystoscopic confirmation of the presence of concretions in the ureters was obtained, and the condition was successfully treated by direct lavage of the ureters.

I have already[2] reported a series of cases of hæmaturia and anuria of short duration occurring in Melanesian natives undergoing treatment for pneumonia; but in none of these did the condition occasion such anxiety as in the case now recorded.

Clinical Record.

A male native of New Britain, aged about sixteen years, was admitted to hospital during an outbreak of an influenza-like disease, when selected patients with incipient pneumonic signs were being treated with "M & B 693". On his admission to hospital on February 14, 1940, the boy complained of cough and pain in the head of one day's duration. His temperature was 103·4° F. and his pulse rate was 80 per minute. Relative dulness and scattered rhonchi were present over the base of the right lung posteriorly. He was given an initial dose of two grammes of "M & B 693", and thereafter he received one gramme every four hours, except that none was given between the hours of 10 p.m. and 6 a.m. On the following day, February 15, 1940, the temperature had fallen to normal, but on February 16 had again risen, reaching 100·4° F. at 10 p.m., and there were now some crepitations at the base of the left lung. On April 17 his temperature was 101·6° F. at 6 p.m., administration of the drug having been discontinued at 2 p.m. following a complaint of abdominal pain. It was also reported that the urine was scanty, but a specimen had not been kept for examination. Seventeen grammes of "M & B 693" had been given during the four days. After this day the temperature fell rapidly and the pulmonary condition cleared up. It is doubtful whether consolidation had occurred. However, a period of complete anuria now supervened, and, as far as could be ascertained by close observation and from the statements of the patient and his friends, no urine was passed between the night of February 17, 1940, and noon on February 24, 1940.

The treatment given was as follows. On February 17 *Mistura Potassii Iodidi cum Tinctura Hyoscyami* was given every four hours; heat was applied to the loins, and a soap and water enema was given. On February 18 the same mixture was given. An enema was again administered and the patient received *Oleum Ricini*. On February 19 the same treatment was given, with the addition of 50 grammes of glucose in 160 cubic centimetres of normal saline solution intravenously. On February 20 the intravenous administration of glucose in saline solution was repeated. On February 21, 500 cubic centimetres of 10% glucose in saline solution were given intravenously. Hot saline solution was given rectally twice, in amounts of 40 ounces. On February 22 rectal administration of saline solution was continued throughout most of the day. Two cubic centimetres of "Salyrgan" were given intravenously. On February 23 magnesium sulphate was given and hot saline solution was administered *per rectum*. Hot drinks were given, as well as two doses of one-tenth of a grain of pilocarpine. None of these measures having produced diuresis, and in view of the possibility of ureteral obstruction, a certain uneasiness was felt in regard to the possibility of the development of hydronephrosis. A radiographic examination was made; but as it was found by a control experiment that acetylsulphapyridine was not radio-opaque, not much help could be expected. No cystoscopic examination was attempted.

The blood urea level on the sixth day of anuria was found to be 180 milligrammes per 100 cubic centimetres. The patient's condition remained good. There was no œdema or evidence of incipient uræmia. Very little pain was complained of. There was some tenderness in the loins and in the hypogastric region. Vomiting was reported occasionally, but did not persist. The boy was generally quiescent, but not particularly drowsy.

On the morning of February 24, the seventh day of anuria, the patient was given half an ounce of brandy every four hours, and three and three-quarter grains of caffein sodium benzoate in solution hypodermically, also every four hours. At about midday on this day he passed four ounces of reddish urine, and after an interval of fifteen minutes a further two ounces. Examination of this urine gave the following results: the colour was reddish opalescent, the filtrate was a clear light sherry colour, the specific gravity was 1,005, and the reaction was acid; it contained a heavy cloud of albumin, but no sugar; spectroscopic bands of oxyhæmoglobin were observed; the urea content was 0·9 gramme per 100 cubic centimetres; the deposit contained fresh red cells and envelopes of red cells, transitional epithelial cells of various forms, no crystals and no casts.

On the evening of this day a further twenty ounces of urine were passed and progress was now uninterrupted; the urine was plentiful and became progressively clearer of abnormal constituents over the next two or three days. The blood urea level on the second day after excretion commenced was 84 milligrammes per 100 cubic centimetres. On March 5, twelve days after the reestablishment of excretion of urine, the blood urea level was 40 milligrammes per 100 cubic centimetres. A urea concentration test (Maclean) produced the following results: (i) prior to the ingestion of urea 107 cubic centimetres of urine were passed, the urea content being 1·5 grammes per 100 cubic centimetres; (ii) one hour after the ingestion of 15 grammes of urea in 100 cubic centimetres of water, 75 cubic centimetres of urine were passed, the urea content being 1·85 grammes per 100 cubic centimetres; (iii) two hours after the ingestion of urea 72 cubic centimetres of urine were passed, the urea content being 2·1 grammes per 100 cubic centimetres.

Discussion.

Pain was not a prominent symptom in this case. This was in contrast to most other cases in my experience; often the patient's outcries have been sufficient to disturb the ward, and morphine has been necessary. Unfortunately, owing to the conditions prevailing and to the large number of admissions at this time, the condition of the patient's urine prior to the onset of anuria is not known. Gross hæmorrhage, such as has been encountered in previous cases, would certainly have attracted attention. Again, had gross crystalline deposits or concretions been directly responsible for the anuria, one would have expected some residuum of crystals in the first urine passed. None were seen. The comparative suddenness with which complete suppression occurred, together with the absence of severe pain, suggests that in this instance the actual mechanical effect of the crystals was small, and that the suppression was largely a reflex nervous phenomenon, as no doubt it is in the majority of cases of anuria associated with hæmaturia due to sulphapyridine.

Acknowledgements.

I am indebted to Dr. E. T. Brennan, Director of Public Health, Rabaul, for permission to publish this communication. I have to thank Dr. H. C. Hosking for radiological facilities, and the staff of the Native Hospital, Rapindik, for the conscientious carrying out of treatment.

References.

(1) G. Carroll, J. Shea and G. Pike: "Complete Anuria due to Crystalline Concretions following the Use of Sulfapyridine in Pneumonia", *The Journal of the American Medical Association*, Volume CXIV, February 3, 1940, page 411.

(2) T. C. Backhouse: "Hæmaturia during Treatment with 'M & B 693'", *The Lancet*, Volume II, 1939, page 736.

Reviews.

A TEXT-BOOK OF PUBLIC HEALTH.

Of its kind, the tenth edition of the "Text-Book of Public Health", by Frazer and Stallybrass (formerly Hope and Stallybrass), is an excellent work of reference, convenient in size, clearly printed and well illustrated.[1] Both authors combine the academic with the practical. Dr. Frazer is the professor of hygiene at the University of Liverpool as well as being medical officer of health to the city and the port of Liverpool, while Dr. Stallybrass, his deputy medical officer of health to city and port, is also a lecturer on public health administration at the university, and on vital statistics and epidemiology at the Liverpool School of Tropical Medicine.

While in matters of detail (especially those relating to public health law) the work contains much that is entirely inapplicable to Australian conditions, it is an inspiring book for anyone interested in public health, and a valuable work of reference. This tenth edition reflects the rapidly altering outlook on the subject of public health. The book began its career in 1874 as a short addendum, entitled "Medical Police", to Husband's "Text-Book of Forensic Medicine". Later editions combined the subjects of forensic medicine and public health, until in the eighth edition in 1915 the union of two rather dissimilar subjects was severed. Fifteen of the chapters of this tenth edition are either new or have been completely rewritten. Among them are those dealing with tuberculosis, genetics, hospital administration and the medical aspects of civil defence against air raids. They are well worth the perusal of those medical practitioners (still numerous) whose conception of the scope of public health is still "drains and diphtheria". The chapter on rehousing and town planning is of particular interest to sanitarians in the older and more closely settled parts of the Commonwealth, where efforts are at last being made to remedy the mistakes of the early days; the maps and letterpress illustrating the principles adopted in rehousing thickly populated areas are particularly worthy of study.

There has been some drastic cutting down on the purely "sanitary" side of the book to keep it within a reasonable compass, but nothing essential has been omitted. The volume is particularly well indexed and can be recommended as a useful addition to any medical library.

[1] "Text-Book of Public Health (formerly Hope and Stallybrass)", by W. M. Frazer, O.B.E., M.D., Ch.B., M.Sc., D.P.H., and C. O. Stallybrass, M.D., Ch.B., D.P.H., M.R.C.S., L.R.C.P.; Tenth Edition, revised and enlarged; 1940. Edinburgh: E. and S. Livingstone. Demy 8vo, pp. 514, with illustrations. Price: 21s. net.

MOTHERCRAFT.

"THE Happy Mother and Child", by Isie Younger Ross, provides a very useful addition to the mothercraft library.[1] The author appears to have enjoyed wide experience in the management of babies and young children, and she mentions many small points the understanding of which will aid the inexperienced mother very materially in the confident handling of her young and growing infant. The book opens with a clear discussion of the antenatal period; but her advice is to stress the importance of antenatal care, not to replace the attention of the doctor. Close cooperation of patient and doctor is urged throughout. There is detailed instruction in the preparation of food and vessels and in the feeding of babies and older children, and there is discussion of foodstuffs and their relative values, together with simple recipes and hints on the serving of food. Management of the child and problems of behaviour are considered, and charts of weight, growth and development present a normal standard against which progress may be checked. Throughout the advice is practical and is clearly put, while there is a number of simple but useful sketch illustrations to illuminate the text. An unfortunate typographical error makes Dr. Vera Scantlebury appear as Dr. Vera Scautebury, but otherwise there is little to criticize. Dr. Eric Pritchard's introduction commends the commonsense value of the book; and we confidently recommend it to those whose work lies in the care of mothers and babies.

NURSING IN ACUTE INFECTIOUS DISEASES.

"NURSING in Acute Infectious Diseases", by Frank V. G. Scholes,[2] is a successful attempt to give nurses a knowledge of the principles they are applying in their work, as well as help and advice in carrying out those principles. Very wisely the author holds that a good nurse will be a better nurse if she knows something of what is going on in the doctor's mind when he orders some particular treatment. All nurses can be divided into two classes, those who use their powers of observation and report their findings faithfully and those who do not. Nurses in the former class will benefit incalculably by the author's lucid exposition of the points to be looked for in the various illnesses. It is taken for granted that the reader is acquainted with general nursing, and no space is wasted in going over this ground, the book being devoted to the special requirements in hospital or home of the infectious diseases.

After a chapter on infection, resistance and immunity, in which he discusses these subjects in an attractive fashion, the author has a chapter on the nature and symptoms of scarlet fever. Then follow four chapters—one on the complications of scarlet fever, one on the principles of the nursing of fever, one on the prevention of spread of infection, and one on the special nursing of scarlet fever. Dr. Scholes has had such a long and practical experience at the Queen's Memorial Infectious Diseases Hospital, Fairfield, Victoria, that his pronouncements may be accepted with confidence. Diphtheria has three chapters, and measles two; other chapter headings include chickenpox, rubella, mumps and influenza; whooping cough; epidemic meningitis; poliomyelitis; and erysipelas.

The book is well printed with large clear type, and has all the principal names and important phrases set up in heavy type, which compels attention. Doctors who treat infectious diseases would do well to read the book, and all nurses should study it carefully. The author is to be congratulated on his pleasant and clear style, which is not without touches of humour, as well as on the completeness of the work.

[1] "The Happy Mother and Child", by I. Y. Ross, O.B.E., M.B., Ch.B., with an introduction by E. Pritchard, M.A., M.D., F.R.C.P.; 1940. Melbourne: Robertson and Mullens Limited. Crown 8vo, pp. 192, with illustrations. Price: 5s. net.

[2] "Nursing in Acute Infectious Diseases", by F. V. G. Scholes, C.M.G., M.D., B.S., D.P.H., F.R.A.C.P.; 1940. Sydney: Australasian Medical Publishing Company Limited. Demy 8vo, pp. 313. Price: 16s., *plus* postage.

The Medical Journal of Australia

SATURDAY, AUGUST 10, 1940.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

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CHEMOTHERAPY.

THAT the introduction of what is known as chemotherapy by sulphanilamide and its compounds has revolutionized the treatment of many conditions and has placed a most powerful weapon in the hands of the medical profession is a statement so obvious that it should perhaps not be made. Be that as it may, the striking power of the weapon and its range of effectiveness are a challenge to the restraint and judgement of medical practitioners in their combat with disease. That the word "pendulum" finds a prominent place in medical literature is a reproach. Someone introduces a new drug or a new procedure; at first no one, maybe, will have anything to do with it, suspicion is cast upon it and its sponsor is disregarded, if indeed he is not subjected to contumely. Then a discovery is made that there is something in the new "fad"; the drug or process is successful; its success is reported again and again. More people become advocates; the despised of yesterday becomes the fashion of today—the "pendulum" has begun to swing, and before long we are told that it has swung too far. Sulphanilamide compounds are so widely used at the present time that it is appropriate to inquire whether the indications for their use are observed as they should be and whether due care is taken in administration lest toxic symptoms make their appearance.

In this issue we publish several important contributions on the sulphanilamide drugs. Dr. Alex. Murphy, of Brisbane, writes on the clinical application and toxic effects of sulphanilamide and sulphapyridine; Dr. A. W. Holmes à Court, in his Listerian Oration, deals with the chemotherapy of pneumococcal infections, making reference to some cases occurring at Sydney Hospital; and Dr. A. G. Cumpston gives a complete account of observations on 80 cases of pneumonia, some of which are mentioned by Dr. Holmes à Court. These articles, of course, do not more than touch the fringe of the subject; but they will direct the minds of readers in a convincing way to the efficacy of the medicament, to the toxic effects that may follow its exhibition, and to the urgent need for care and for that restraint and judgement already mentioned.

Turning first to the efficacy of sulphanilamide compounds, we find that they are effective in one type of infection and not so effective in another; naturally, therefore, we ask how these drugs act. This question has been discussed in these pages on previous occasions, and while it is not necessary to make an attempt to cover the whole subject, we would refer readers to two previous discussions. In the issue of April 23, 1938, the observations of E. E. Osgood were recorded.[1] Osgood held that the major action of sulphanilamide was to neutralize or to destroy toxins and to cause a diminished rate of bacterial division. He thought that by this action, though it did not kill the microorganism, it enabled the bactericidal action of human serum and the phagocytic action of the neutrophile cells and monocytes of the marrow and blood to overcome the infection. On April 29, 1939, attention was drawn in these pages to an important contribution by J. McIntosh and L. Whitby[2] which is worthy of study. These observers carried out experiments with "M & B 693" and expressed the opinion that the drug possibly destroyed some essential food substance or enzyme necessary for multiplication. This work is interesting in view of a recent communication by J. S. Lockwood and H. M. Lynch,[3] who conclude that the drug acts in some way through interference with the ability of the bacteria to utilize the traces of assimilable nitrogen in whole blood, serum, urine or other body fluid. It is possible, they think, that sulphanilamide combines in some way with the free aminonitrogen of protein degradation products and renders them unsuitable for bacterial utilization. This point they are still investigating. It is perhaps worth recording here that Lockwood and Lynch's hypothesis is, in their opinion, consistent with the spectacular effects of sulphapyridine in pneumonic infections, "because of the minimal tissue injury in pneumococcic pneumonia". Apart from the scientific interest of all the work that has been done, and the fascinating hypotheses that may be based on it, what concerns the present discussion is that in chemotherapy the therapist is using an agent that interferes with complicated body processes and is not merely introducing so much chemical substance that will slay bacteria as they thrive in some organ of the body.

The toxic effects of these drugs are described by Dr. Alex. Murphy. As the result of recent investigations, W. H. Brown, W. B. Thornton and J. S. Wilson have concluded that sulphapyridine is essentially more toxic than sulphanilamide—they found that serious toxic manifestations occurred twice as often after the former had been given than after the latter. They regard rashes and fever as useful signs of toxicity, in that they may act as warnings of more serious complications. That such a serious condition as agranulocytosis may follow the administration of a drug of the sulphanilamide group is sufficient ground for insistence on the greatest caution in

[1] *The Journal of the American Medical Association*, January 29, 1938.
[2] *The Lancet*, February 25, 1939.
[3] *The Journal of the American Medical Association*, March 16, 1940.

its use. A great deal more might be written about the toxic effects sometimes caused by these drugs, their value might be extolled at greater length, and scores of authors might be quoted in each branch of the subject. This is neither necessary nor expedient. What is quite clear may be stated shortly under two headings: first, that we have at hand an extremely powerful agent capable of curing severe bacterial infections, hitherto uninfluenced by drugs, and at the same time capable of causing dire untoward effects; secondly, that we have not discovered how this powerful agent produces its effects.

From the foregoing it would appear that there is little need to make a plea for care, for restraint and for judgement. Unfortunately the pendulum already mentioned has swung much too far in the wrong direction. Sulphanilamide drugs are being used with exuberance and extravagance. Honorary medical officers of hospitals report that resident physicians and surgeons are using them as a "pot shot in the dark", without any real indication that they are necessary, and pharmacists tell of the enormous numbers of prescriptions for these drugs from general practitioners. Large quantities have been bought over the counter by the general public. Fortunately a recent regulation makes it impossible for the general public to buy sulphanilamide without a prescription from a medical practitioner, a dental surgeon or a veterinary surgeon. But this regulation was introduced at the instance of the Director-General of Medical Services to conserve stocks for the army and not to protect the public against its own ignorance and foolishness—democracy will not interfere with the freedom of the individual by preventing him from buying certain harmful drugs that he may consume at his own sweet will and pleasure. Medical practitioners (with dentists and veterinarians) now have the matter in their own hands—if they pursue therapeutic wisdom, they will achieve cures and possibly add to the knowledge already gained in this fertile field; if they prefer indiscriminate empiricism, they will often do harm where good should follow, they will bring discredit on a useful remedy and they will prevent the growth of knowledge.

Current Comment.

THE DANGERS OF COSMETICS.

FROM time immemorial women have plied their bodies with extraneous substances as aids to beauty. This practice is by no means confined to civilized people. Savages smear their bodies with clay, daub themselves with vegetable dyes, powder their hair with lime, and so forth. And it is not only women who use cosmetics. Men oil their hair, massage their faces with pomades, and apply face powder after shaving; some use hair dyes and some resort to even more extensive measures of beautification. But women—that is, civilized women—are more firmly enslaved to fashion than men are, and they are apt to go to extremes at the dictates of this inconstant mistress. If fashion says that a woman's nose must be purple and her ears green, they will be so; and hosts of women will think not at all of the possible dangers of the dyes they use, so long as their noses are a rich shade of purple and their ears the correct emerald or jade. The injurious effects of certain cosmetics have been pointed out on many occasions. Recently the subject has been reviewed by George L. Wolcott in a paper that is worthy of comment in view of the almost universal use of cosmetics by civilized women today.[1] Wolcott points out in the first place that the incidence of injury from cosmetics is very low, but is impossible to determine because of the absence of authentic statistics. Many of the earlier injuries were systemic poisonings by dangerous substances, such as lead and mercury; but reputable manufacturers no longer use these harmful materials; in fact many manufacturers maintain laboratories to ensure that their products shall remain free of poisonous or harmful substances. However, there are people (Wolcott calls them "cosmetic racketeers") who use such ingredients as will make the most elegant preparation, regardless of any potential dangers that they may possess.

Wolcott quotes Carleton as stating that toilet powders may contain vegetable powders, such as rice, wheat and corn flour, starch, acacia and tragacanth; mineral powders, such as chalk, talc, kaolin, magnesium carbonate, bismuth nitrate, bismuth carbonate and zinc oxide; vegetable or aniline dyes; various ethereal oils as perfumes, and orris root as a fixative. He draws attention to the "increase in the apparently allergic reactions to certain ingredients of face powders, notably orris". Various authorities have drawn attention to the importance of orris root in the cause of hay fever and other allergic manifestations.

Cold creams are said to be prepared from a vegetable or mineral oil, such as almond oil, yellow wax or liquid paraffin. A small quantity of sodium borate is added to aid emulsification. Palmitates, stearates and fatty alcohols may or may not be present. So-called cleansing creams are mixtures of liquid paraffin and fats and waxes with a higher melting point. According to Wolcott, most of the substances employed in the manufacture of creams are relatively innocuous. McKenna has suggested that paraffin in cold cream may cause rodent ulcer and epithelioma and that the physical action of both cold cream and vanishing cream may cause rosacea.

Lipstick has as its basis several of the following: yellow wax, paraffin, "Vaseline", hydrous wool fat, castor oil, stearic acid and cetyl alcohol. Various perfumes, lakes and dyes are added. A number of cases of skin sensitivity to the dyes have been recorded. Dermatitis due to hydrous wool fat in lipstick has also been noted. A commonly used synthetic perfume, methylheptine carbonate (derived from castor oil), has been found to cause dermatitis.

Wolcott quotes *The Journal of the American Medical Association* as stating that "Nail lacquers are solutions of nitrocellulose in various solvents, with the addition of certain aids to solution and plasticizers to make the film flexible". Acetone, butyl acetate and amyl acetate are used as solvents; toluene, benzene, xylene and naphtha are used as aids to solution; castor oil, camphor and rosin are used as "plasticizers". These nail lacquers are among the least harmful of the cosmetics. They frequently cause brittleness and splitting of the nails; but apparently they are seldom responsible for anything more serious or uncomfortable. One authority has suggested that they may actually be of value by virtue of their antiseptic qualities, preventing infection that might be introduced by the "none too sterile operating tools of the manicurists".

Hair dyes include vegetable dyes, such as henna; metallic dyes, the metal of which combines with the sulphur of the hair to form a deposit of metallic sulphide; compounds of metallic salts and vegetable products, such as pyrogallic acid; and aniline derivatives, the best known being paraphenylenediamine.

Of all the cosmetics, the hair dyes are the worst offenders. Not only are simple irritations reported throughout the literature from the use of hair dyes, but the most severe of systemic poisonings are reported and in an unusually large number of cases. The story of poisoning by hair dye is not a new one.

The dangers of the metallic dyes and paraphenylenediamine are so well known as to need no further mention here.

Dermatitis, hay fever and asthma have been noted as a result of the employment of wave-setting preparations,

[1] *Archives of Dermatology and Syphilology*, January, 1940.

which are mucilaginous substances used for producing or setting waves in hair. Hay fever and asthma are said to be caused by the gum in the preparation.

Eyebrows and eyelashes are darkened by painting with mascara or lamp black, or by actual staining with a hair dye. A substance known as "Lash-lure" was responsible for a series of tragic happenings about 1931. Its dangerous ingredient was paraphenylenediamine. It caused corneal ulceration and in at least one case death.

Women and men have used perfumes to mask the unpleasant odours that arise from a body that has not recently encountered soap and water. Now that bathing has become the rule, the need for them is not so great; but they are used with perhaps greater freedom than ever. Modern perfumes are mainly synthetic and are derived principally from coal-tar products. Wolcott draws attention to a condition of "photopigmentation" that results from the use of certain perfumes. The offending substance is said to be oil of bergamot.

Most depilatories contain barium sulphide; but the sulphides of calcium, strontium, sodium and magnesium are also used. At one time thallium acetate, a dangerous poison, commonly used to kill rats, was incorporated in some of the depilatories on the market. One of these, we are told, "rode to fame not on its beneficial effects but on the widespread destruction it caused its users". According to Winters, "Baldness, skin injury, nervous and glandular troubles were some of the effects produced by Koremlu".

Wolcott mentions that within recent years vitamins have been introduced into cosmetics. He states that they will probably do little if any harm; "moreover, their efficacy will parallel their harmfulness".

This review of Wolcott's paper is made with the object of drawing attention to the numerous substances in cosmetic preparations that may have harmful effects. Most medical practitioners nowadays have learnt to suspect the existence of an allergic state when they encounter a dermatological disorder that might have been associated with an external application; but it is worth while their remembering that some materials for external application contain substances capable themselves of causing local or systemic harm.

THE USE OF SULPHANILAMIDE IN GONORRHŒA OF THE MALE.

In a discussion in these pages in February, 1939, on the use of "Uleron" in the treatment of gonorrhœa the hope was expressed that Australian practitioners would record their results in the treatment with sulphanilamide compounds of patients suffering from gonorrhœa in both the early and late stages. Since that time two contributions have been published in this journal—one by N. M. Gibson and C. J. Wiley in May, 1939, and the other by V. N. B. Willis in January of this year. An interesting account of the use of sulphanilamide and allied drugs in the treatment of gonorrhœa in the male has now been given by J. H. Abbott in the report for 1938 of the Director-General of Public Health of New South Wales. This report, by the way, though covering the twelve-month period ended December 31, 1938, was not ordered by the Legislative Assembly of New South Wales to be printed until March, 1940.

The details of treatment set out by Abbott are of interest and will probably be of practical use to medical practitioners, especially if considered in conjunction with a discussion on the new outlook on gonorrhœa appearing in these pages on July 6, 1940. At first the method of giving sulphanilamide in one or more short courses of from three to five days' treatment was adopted, the daily dose in every instance being four grammes. It was soon discovered that while the response in late cases was both dramatic and tolerably certain, the results became less satisfactory as the earlier infections were treated. An increased dosage of five grammes a day for five days gave better results; but it was not until longer courses were substituted for shorter ones that an appreciable increase in the proportion of quick cures in early cases was obtained. In the cases reviewed by Abbott a course of ten days' continuous treatment was adopted, and he adds that even longer courses are now being employed. When the short courses were used there were practically no toxic reactions. Over 1,200 patients were treated in this way and the only toxic symptoms were slight nausea, an occasional attack of vomiting and on extremely rare occasions mild cyanosis. When the patient failed to take the proper course of treatment, failure was due to disinclination rather than inability to take it. When ten-day courses were introduced toxic results became more severe and more frequent. Giddiness, inability to concentrate, lassitude and somnolence were frequent complaints. Cyanosis was more pronounced and slowing of the mental processes and lack of alertness were frequently noticed. None of these symptoms was regarded as an indication for the discontinuance of the drug. Administration of the drug was withheld only in the presence of severe cyanosis with pallor, of air hunger or of skin eruption. In regard to skin eruption, Abbott points out that, in Australia especially, many patients develop a photosensitivity and that all patients should protect themselves as much as possible from the direct rays of the sun. Though in one place he states that the longer chemotherapy is delayed, the greater will be the number of cures that may be expected when it is introduced, Abbott makes the statement that chemotherapy should be introduced as soon as possible. He has not noticed that early chemotherapy that proves a failure gives rise to a greater proportion of chronic cases. He has often observed, however, that failure in one course may be followed by failure in subsequent courses. He believes that irrigation of the anterior part of the urethra should be started as soon as the patient comes under treatment; posterior irrigation is seldom, if ever, indicated.

It will be noted that Abbott is in agreement with Gibson and Wiley and with Willis that local treatment should be used in addition to chemotherapy. Willis also believes that chemotherapy should be started at once—"because we may abort the infection if it should be acute". The doses used by Willis—0·5 gramme three times a day—are much smaller than those recommended by Abbott.

A further practical consideration will be mentioned. The rapid disappearance of symptoms under chemotherapy is likely to produce "carriers" unless a strict standard of cure is adopted. J. Cooper Booth, the director of the Division of Social Hygiene in the New South Wales department, draws attention to this danger and states that since sulphanilamide has been used in the department the number of "defaulters" has increased. G. Hayes, the medical officer for venereal diseases in the Queensland health service, also insists in the last departmental report that there is a "definite tendency for this drug in certain cases to convert an obviously infected patient into a symptomless 'carrier'". The practical consideration that arises is the adherence by the attending practitioner to a standard of cure. The apparent absence of symptoms is not a sufficient guarantee that the disease has been overcome, even if no discharge becomes evident after the provocative passage of sounds. The examination of smears made from secretions of the prostate or seminal vesicles may suffice, but the complement fixation test is the most reliable guide and should be generally adopted. As was stated in our recent discussion on gonorrhœa, the public dread of the disease is less than it was, and patients readily mistake disappearance of symptoms for cure. The medical attendant must be careful that he does not unconsciously adopt the same attitude of mind. There is some justification for Cooper Booth's statement that venereal diseases are the province of the skilled specialist; but patients suffering from gonorrhœa still visit the general practitioner and, provided the practitioner is careful to adopt reliable tests of cure, there is no reason why he should not give the patient treatment.

Abstracts from Medical Literature.

THERAPEUTICS.

Combined Therapy in Subacute Bacterial Endocarditis.

THE intensive use of chemotherapy in the treatment of subacute bacterial endocarditis has demonstrated its definite but temporary benefit. The main problem is the fact that the vegetation, chiefly a mass of fibrin and platelets, provides an ideal culture medium for the organisms; leucocytes are found in the vegetation. Saul R. Kelson and Paul D. White (*The Journal of the American Medical Association*, November 4, 1939) have suggested the addition of crystalline heparin to prevent further thrombotic deposition on their surface in order (*a*) to restrict the nidus and culture medium for bacterial growth, (*b*) to prevent embolism for the freeing of fresh thrombus, and (*c*) to check the growth of the vegetations so that proliferating fibroblasts may fill in the areas thus limited. Heparin is administered by uninterrupted intravenous drip day and night for fourteen days; the contents of a 10 cubic centimetre vial (10,000 units) are added to 500 cubic centimetres of normal saline solution. The rate of flow is carefully regulated to maintain as far as possible the venous clotting time (normally below twenty minutes) at approximately one hour. Heparin administration is begun four to seven days after the commencement of the sulphapyridine administration, a blood level of five milligrammes per hundred cubic centimetres or more being maintained by a daily dosage of four to five grammes. This part of the treatment is continued for four weeks in all. Blood transfusions are given if the red cell count is below 3,500,000 cells per cubic millimetre. Saturation with ascorbic acid by oral administration of 200 milligrammes four times a day for three days is maintained at 100 milligrammes a day. Seven case histories are presented, and although two of the patients died before the treatment could have influenced the disease, three have shown remarkable periods of freedom from symptoms—nearly five months in one instance. An analysis of 246 follow-up cases shows that a period in excess of five weeks is rare. Although the danger of the treatment is recognized, this combined therapy gives the authors more promise than any other method they have used or of which they have heard.

Desoxycorticosterone Esters in Addison's Disease.

THE two important recent advances in the treatment of Addison's disease are correction of disturbances of electrolyte metabolism by administration of large amounts of sodium chloride, and the elaboration of extracts of adrenal cortex. Despite these advances, the patient suffering from Addison's disease has been only moderately relieved. J. W. Ferrebee *et alii* (*The Journal of the American Medical Association*, November 4, 1939) describe the results of the administration to thirteen patients of synthetic esters of desoxycorticosterone. This follows the isolation of two series of crystalline steroids from the adrenal cortex. Observations were made of the effects of the administration on various blood constituents, including sodium, potassium, calcium, chloride, bicarbonate, non-protein nitrogen, serum proteins, sugar and cholesterol; the effects on excretion of water, sodium, potassium, total nitrogen and riboflavin were studied; also the effect on the basal metabolic rate and carbohydrate metabolism was noted. Caution must be observed in the administration of these esters, as excessive amounts will lead to hypoproteinæmia, marked œdema or cardiac insufficiency. On the other hand, clinical improvement takes place that is greater than in any form of therapy so far initiated. There is a striking retention of salt and water, so that the serum sodium concentration increases to normal and is maintained as fluid retention continues. Serum potassium concentration is decreased to an abnormally low level. The non-protein nitrogen level in the serum decreases even when it is normal at the commencement of the treatment. There is no effect on the carbohydrate metabolism. The blood pressure rises gradually, although this result is not so rapid in its appearance as the other effects; it may increase to the hypertension stage. The morning asthenia and nausea disappeared during the course of therapy. No definite effect in pigmentation has been noted. There is great variation in the effective dosage, but the following dosage was used as a routine for the purpose of this study: 25 milligrammes of desoxycorticosterone acetate or propionate were given daily for four days, then 10 to 25 milligrammes were given daily for five days more. The hormone dissolved in sesame oil was injected subcutaneously or intramuscularly once a day, and each cubic centimetre contained five milligrammes.

Hypoparathyreoidism.

H. F. NEWMAN (*The Journal of the Mt. Sinai Hospital*, March-April, 1940) describes the treatment of a woman who was suffering from long-standing tetany following subtotal thyreoidectomy. Huge doses of calcium and parathormone gave no relief. The patient had active symptoms of tetany with a serum calcium figure of 10. The author declares that mild cases of hypoparathyreoidism respond to a diet low in phosphorus and high in calcium, supplemented by calcium lactate. In severe cases these measures are not reliable. Parathyreoid extract has several disadvantages: expense, short duration of its effect (six to twelve hours), demineralization of bones due to liberation of calcium. Vitamin *D* and calcium given by mouth are valuable; 300,000 units of crystalline vitamin *D* remove symptoms and restore serum calcium to normal. By the action of ultra-violet rays on ergosterol, various sterols have been produced, and these affect calcium and phosphorus metabolism. Of these, dihydrotachysterol, marketed as "A.T.10" (antitetany factor), are used to increase blood calcium. Crystalline vitamin *D*, vitamin D_2 (calciferol), has the same effect, but is slower in action. One cubic centimetre of "A.T.10" represents 40 units of parathormone. The action of "A.T.10" given by mouth begins after two days, with maximum effect in four to seven days and the end effect in one to three weeks. Calcium salts, 30 grains of calcium lactate, are given by mouth and 10 to 20 cubic centimetres of calcium gluconate are given hypodermically per day in severe tetany in addition to daily doses of one cubic centimetre of "A.T.10" for some weeks. In this way the symptoms were relieved and the blood calcium was raised from eight to ten or fourteen milligrammes *per centum* in the case referred to. However, the blood serum figure fell to 10 and symptoms recurred on suspension of "A.T.10" and parathormone, of which 2,400 units were given in forty-six days. Eventually the patient retained good health by taking 35 grains of calcium daily.

Antacids.

D. WYLLIE (*Edinburgh Medical Journal*, May, 1940) discusses the influence of certain antacids on the acidity of the gastric juice. Crohn showed that small doses of sodium bicarbonate (20 grains) exert no neutralizing action; larger doses do, but this is followed by a great secondary stimulation of acid secretion. Other alkalis have a similar effect. Twenty-four patients have been tested by fractional test meals and have been treated with milk and various alkalis. So long as free acidity in the test meal is below 40 clinical units, that is, within normal limits, hourly milk feeds of three ounces effect complete acidity control; but when hyperacidity is present milk feeds are inadequate. In these cases Sippy powder number 1 or 20-grain doses of magnesium trisilicate or of tribasic magnesium phosphate were given. The effects lasted thirty minutes; after this there followed an increased acid secretion. The effect of magnesium trisilicate lasted forty-five minutes. Hourly doses of these three preparations were then tried between milk feeds. The results were unsatisfactory in the control of acid secretion; magnesium trisilicate was the most successful antacid. Single drachm doses were then tried. Aluminium hydroxide controlled acidity for one and a half to two hours without undesirable effects, magnesium trisilicate for one and a half hours, with some tendency to greater secretion afterwards, and Sippy powder number 2 for less than an hour, with secondary stimulation of acid secretion in half the cases. The results suggest to the author that satisfactory control of free acidity can be expected by the administration of two-hourly milk feeds of six ounces with one drachm of aluminium hydroxide or magnesium trisilicate half an hour after the feeds. By this means acidity can be controlled for eighteen out of the twenty-four hours, and this would allow seven or eight hours of uninterrupted sleep at night.

Ménière's Syndrome.

J. H. TALBOT AND M. R. BROWN (*The Journal of the American Medical Association*, January 13, 1940) describe the treatment of Ménière's syndrome. It has been said that in this condition there is a collection of fluid endolymph, that there is a waterlogged labyrinth, or that a retention of sodium salts occurs. The blood of forty-eight patients was investigated for sodium, fixed bases and protein, but no consistent abnormality was noted. Even after low sodium diets there was no significant change in the serum, and consequently no evidence that gross retention of water or salt incited the attacks. Further experiments included the ingestion of large amounts of water and salt, in order to try to induce the attacks, but without success. Forty patients were treated with six to ten

grammes of potassium chloride in an aqueous solution daily. All were benefited, though none was cured. Several of these patients had tried to follow the low sodium regimen with ammonium chloride, with ill success. Several patients ceased taking the high potassium diet, with exacerbation of symptoms, to find that symptoms became less when they returned to the diet.

NEUROLOGY AND PSYCHIATRY.

Acute and Subacute Necrotic Myelitis.

J. G. GREENFIELD AND J. W. ALDREN TURNER (*Brain*, September, 1939) report in detail one case of acute and two cases of subacute necrotic myelitis. They discuss the clinical and pathological findings in these cases in the light of material originally reported in 1926 by Foix and Alajonaine. The picture is one of progressive amyotrophic paraplegia with dissociated sensory changes, loss of the tendon reflexes and of sphincter control. The cerebro-spinal fluid shows an increase of protein with no evidence of spinal block. Differential diagnosis from *neuromyelitis optica*, Pott's disease and the compression syndromes is discussed. The condition is essentially a primary obliterative sclerosis of the small intramedullary and meningeal vessels in the lower segments of the cord.

Insulin Shock Therapy in Korsakoff's Psychosis.

P. C. TALKINGTON AND T. H. CHEAVENS (*The Journal of Nervous and Mental Disease*, February, 1940) report a case of Korsakoff's psychosis rapidly cured by insulin shock. The patient was a female, aged thirty-four years, with a pre-alcoholic schizoid personality. Insulin was administered in small doses over a period of eleven weeks, causing forty-seven reactions in the form of coma and sweating. The mental condition cleared except for a residual circumscribed amnesia covering a period of two months. The authors believe that, despite the obvious organic factor, this disease is predominantly "functional" and closely related to the biogenetic psychoses. They find insulin valuable in facilitating the assimilation of glucose and stimulating the metabolic process. The sweating during the coma aids elimination, and the insulin itself produces valuable sedation.

Neuro-Psychiatric Disorders Occurring in Cushing's Syndrome.

CUSHING in 1932 described a disease which he termed pituitary basophilism, consisting of a rapidly developing and painful adiposity, sexual dystrophy, hypertrichosis, kyphosis, lumbo-spinal pains, fatigability and ultimately extreme weakness. N. S. Schlezinger and W. A. Horwitz (*The American Journal of Psychiatry*, March, 1940), in reviewing the literature relating to this condition, find that mental symptoms occur not infrequently. Depression is the most prominent feature of such symptoms. These authors describe the clinical and post-mortem findings in a case of Cushing's syndrome occurring in a woman of twenty-seven years, with marked depressive and self-condemnatory ideas and evidence of extrapyramidal disease of the central nervous system. The condition remained unchanged until the patient died following left suprarenalectomy. The post-mortem examination revealed a small right suprarenal gland, a benign neoplasm of the left suprarenal, and hyaline changes in the basophile cells of the adeno-hypophysis with congestion and œdema of the brain parenchyma and focal areas of encephalomalacia in the frontal lobes. The authors suggest that the ætiology of this complex disorder may be a neuro-endocrine one on an encephalitic basis. They stress the relationship to manic-depressive and the involutional psychoses, and suggest that evidence of Cushing's syndrome should be sought among the large group of depressive patients confined in mental hospitals.

Paraphyseal Cysts of the Third Ventricle.

THE report of a benign cyst in the third ventricle of a youth, aged seventeen years, is made by Howard Zeitlin and Ben. W. Lichtenstein (*The Journal of Nervous and Mental Disease*, June, 1940), who, in reviewing the literature, claim that these cysts arise from the *velum transversum* in the most anterior part of the roof of the third ventricle of the brain from an embryonic *Anlage* of the paraphysis. In its early stages the growth may produce no symptoms; later there will occur severe headaches, sudden in onset or intermittent in character, associated with vomiting, drowsiness or hypersomnolence, disturbances of vision and epileptiform seizures. In the last stages of the illness there may be sudden loss of consciousness, mental disturbances and hyperthermia. Disturbance of vision occurs through pressure on the optic chiasma by the bulging of the floor of the third ventricle. The mental changes and progressive dementia are probably due to an increasing secondary hydrocephalus. Obesity, polyuria, hyperglycæmia and other vegetative symptoms are rarely observed. The patient whose history is reported in this communication, died within a few days after a provisional diagnosis of epidemic encephalitis had been made. The cyst was revealed at the necropsy.

Faulty Detoxication in Schizophrenia.

J. H. QUASTEL AND W. T. WALES (*The Lancet*, March 2, 1940) produce evidence corroborating their statement made in 1938 that schizophrenic patients in a state of catatonia appear to be unable to detoxicate benzoic acid at the normal rate. In their original experiments they made use of Quick's test of liver function, wherein the excretion of hippuric acid is measured after a standard dose of benzoic acid has been given by the mouth. Now, by administering sodium benzoate intravenously, they have established that the lowered rate of excretion of hippuric acid among catatonic and certain other psychotic patients is not necessarily due to faulty absorption of benzoate from the gut.

Results of Shock Therapy in the Treatment of Affective Disorders.

DAVID C. WILSON (*The American Journal of Psychiatry*, November, 1939) states that he has administered "Metrazol" ("Cardiazol") shock treatment to patients suffering from affective disorders. He believes that while a large percentage of these patients recover spontaneously, any treatment is justifiable that will shorten the course of the illness or facilitate the nursing of it. Shock treatment is useful because the maniacal patient becomes quieter after the second or third administration and can, therefore, be nursed in a general hospital. A follow-up study was made of these patients six months after discharge from hospital. It disclosed that 76% remained improved and 41% were greatly improved. The author found that a few convulsions were often beneficial when used in conjunction with other forms of treatment in the mixed forms of depression, especially at the involutional period.

Convulsion Therapy of the Psychoses.

ANDREW M. WYLLIE (*The Journal of Mental Science*, March, 1940) discusses the use of the analeptic drugs, "Cardiazol" and "Triazol", in the treatment of 144 psychotic patients. He considers the treatment to be generally safe, the mortality being only 0·54%. Various fractures and dislocations are common complications, and vertebral compression fractures occur, but are not, in the opinion of the author, accompanied by grave consequences. The risk of activating latent pulmonary tuberculosis by convulsion therapy is noted and may be minimized by a more careful selection of patients, by the use of the sedimentation test and radiography. Prolonged amnesia occurred in some cases, but was not generally serious. Prolonged rise of blood pressure was observed in many instances. The author considers "Triazol" more effective than "Cardiazol" in producing stable remissions.

Psychoses with Myxœdema.

RALPH M. CROWLEY (*The American Journal of Psychiatry*, March, 1940) comments on the rarity of psychoses associated with myxœdema, and reports two cases in detail. The first patient was a woman of thirty-eight years, who, four years after the establishment of an artificial menopause, complained of swelling of the face, neck and limbs, with weakness, palpitation, dryness of the skin and a feeling of coldness. In addition she showed a depressive paranoid reaction, which responded to thyreoid therapy. The second patient was a woman of sixty-five years, who suffered from hallucinations and agitation. She had a dry wrinkled skin and an adenoma of the thyreoid gland. Her basal metabolic rate was −20%. She complained of the cold, was depressed and believed herself persecuted. Her condition improved under thyreoid medication, but relapsed after an attack of influenza. Later on she recovered and has remained well without further thyreoid treatment.

Protracted Shocks Occurring during Insulin Therapy.

FRITZ KANT (*The Journal of Nervous and Mental Disease*, June, 1940) discusses the problem of protracted shock occurring as a complication of insulin therapy, and believes that the condition indicates something more than hypoglycæmia, hypochloræmia or dehydration—a condition creating an inability of the tissue cells to utilize sugar. He believes that protracted shock may be avoided by shortening the duration of deep coma; that the time factor is more important than the insulin dose. Though the protracted shock may last for hours or days and become alarming in its clinical manifestations, it frequently appears to have a favourable influence upon the psychotic state. There is no specific treatment for protracted shock. Each shock must be treated symptomatically.

Special Articles on Psychiatry in General Practice.

(Contributed by request.)

VI.

HYSTERIA.

HYSTERIA throughout the ages has been one of the mystery diseases, in this respect being akin to that other mysterious malady, epilepsy. It is only in modern times that the veil has been lifted from these strange disorders of behaviour and the cause elucidated, in the case of the former completely, in the case of the latter partially. Physicians have at all times recognized to some extent that the phenomena of hysteria were the result of mental states, the word mental being used here in a wide connotation, and that behind the morbid behaviour there was a goal of some kind. But it was left to the painstaking researches of the late Professor Freud to discover what the goal was, and to uncover the psychopathology of the disorder.

A thorough understanding of the psychopathology of hysteria is absolutely necessary before any comprehension of the mechanism of other psychoneurotic and even psychotic conditions can be understood.

The fundamental concept of all these disorders is that they have a meaning for the individual. They subserve a limited purpose in his life struggle; in fact they differ from organic diseases in that they present a teleological aspect, whereas organic disease can be looked upon as accidental or the end product of degenerative changes.

Hysteria and the other psychoneuroses are not only diseases in the ordinary sense, but are also disorders of man's social behaviour; they are reactions, faulty as they may be, to man's social and familial environment, and in that respect they can be looked upon as the results of ignorance of the effects on the human race of the social *milieu* that the race itself has created. In the long upward struggle from his primitive state man has been forced to renounce many modes of behaviour which gratified his desires in former times and in other environments. But the mental apparatus has not always been equal to its struggle with the frustrations imposed by the social code, and various mechanisms have been evolved either to controvert the pain of these frustrations or to side-track them. Some of these side-trackings may have and still do serve socially useful purposes; but others serve no socially useful purposes; instead they render the individual socially inefficient. One of these mechanisms is hysteria.

Psychopathology of Hysteria.

The foundation of society through the institution of marriage, even in its most primitive forms, has necessitated the frustrations of some of the components of the sexual instincts and the direction of the sexual function into certain definite channels above all others. The growth of religio-moral ideas has frowned upon all manifestations of sex outside of marriage and relegated them into categories of sin.

So strong and persistent has been this pressure and demand of our educational system, bearing as it does with its greatest severity upon the early formative years of childhood, that our mental apparatus has had to devise a means of protecting itself from even the memory of many childish activities, more especially those which could be termed sexual; we call this mechanism "repression". It is a common function of the mental apparatus and a necessary derivative of the conflict between the infantile pleasure-pain principle of mental reaction and the adult principle of reality functioning. I shall return to this later on.

Before we can hope to understand the psychopathology of hysteria, certain concepts must be accepted as valid, even though the concepts themselves may not be in the form that can be considered definitely and finally settled. The first concept is that of the "unconscious"; this word has given rise to much controversy and not a few have had grave difficulty in accepting it. It seems, however, to anyone who has made an objective study of the humans around him and an introspection of his own mental life, that the term unconscious as applied to a category of the mental apparatus is obvious. That there is mental activity beyond the sphere of consciousness is undoubted, and the mental activity in that sphere is of considerable quantity but of different quality from that of consciousness. As a matter of fact it is really more difficult to understand the fact of consciousness. The fact of self-awareness is so unique, as far as can be ascertained in animal life, that it is a far more difficult concept to understand. The unconscious consists of mental images or memories of all those trends which during the early period of life, the first four or five years, served as means of pleasurable gratification or acted as methods of libidinous excitement or of those impulses of aggression which arise as the result of the frustration of these manifestations of libidinous pleasure. From the reservoir of that primitive mental apparatus called the "id" from which all these tendencies flow, there arises as a result of the conflict of these primitive trends with the child's culture environment a modification called the "ego", a mode of mental functioning which deals with the real social world and which exercises a controlling function both internally and externally. The former, being automatic, is called "repression"; the latter, being dynamic, is called the will. All that is repressed forms the unconscious; it may even be that there are, as Jung claims, not only individual memories in the unconscious but also racial memories, inherited precipitates of the past cultural struggles.

This brings us to the second concept, repression, which we have seen is a function of the ego. It acts unknown to us, has grown unknown to us and is really the invisible force of our cultural *milieu*. It is this force that is lifted to some extent in anger, in dreams, in alcoholic intoxications and in the psychoneuroses and psychoses. The concept of repression is difficult to grasp and its formulation in words is a task that requires considerable skill; but without this concept the psychopathology of hysteria is impossible to formulate. We can liken repression to the pressure of the atmosphere which, although unseen and unnoticed directly, yet is responsible for many of the facts observed in Nature. Repression is the invisible force of cultural society, a force that has phylogenetic roots as well as ontogenetic roots, for we are born, as before observed, with some sort of mental precipitate of the immemorial past with all its trial and errors, with all its terrors and horrors. Repression manifests its greatest activity during those early years when each human being reproduces ontogenetically his mental phylogeny, the first five years of his life when he has to give up so much and bend his mental apparatus to the pressure of his cultural surroundings.

Symbols.

Symbolization follows almost automatically from the concept of repression. An urge in the unconscious is denied direct expression—its way to ideation or motor activity is barred by repression—it seeks expression in a vicarious manner. The human phallus can be seen as a snake, but not as an integral part of human anatomy. A bridge can be seen as a structure uniting two other structures when the idea of coitus is incompatible with the forces of consciousness. Symbols have been used from time immemorial in folk lore, religion, art *et cetera*, and no one found such methods of expression anything else but "natural"; but when the theory of symbols was applied to human disorder, to dreams *et cetera*, stronger opposition was encountered.

The Concept of Pansexualism.

The concept of pansexualism is probably Freud's particular original contribution, for it at any rate was the one that called attention to his work and made his name notorious before it became famous.

Pansexualism is not altogether a good name for the theory that the whole body has an investment of libido,

that all organs and structures can be and are invested with sex energy and that this libido is largely labile, that is, it can flow into and flow out of an organ.

It is in the early years of life that the libido has its greatest power of movement; it is not until the supremacy of the sexual organs is finally established that this instability of the libido is greatly lessened and the greater part becomes bound in the sex organs themselves and serves to fulfil its pre-ordained biological aim of reproduction.

Prior to this the libido is attached to zones such as the oral and the anal zones, the skin *et cetera*, and gives to the activities of these zones that special feeling tone which we only vaguely recognize as sexual in the adult.

In certain adults the sexual aim is frankly and solely directed to the obtaining of gratification through the activity of one of the many zones other than the strictly sexual zones or organs, and we then call such manifestation a perversion, masturbation, homosexuality, exhibitionism, cunnilingus *et cetera*. These manifestations of the sexual life have all been part of the normal activity of the child at some period or other, but have become repressed in the great majority of instances through the growth of the ego and thus have become part of the unconscious. The sexual life of the infant thus has been, as it is termed, polymorphous perverse.

Now it is easy to pass from this to the concept of hysteria. The phenomena of hysteria are the expression in the soma of the perverse tendencies and other forbidden desires of the individual—tendencies which under the stress of internal or external excitement or frustrations have become too powerful to be altogether repressed, but gain a vicarious satisfaction in a symbolic manner by organic symptoms such as paresis, contracture, fits, aphonia *et cetera*.

But the individual knows nothing of this consciously—for the idea of these perverse and forbidden desires is altogether foreign and abhorrent to consciousness and is excluded permanently therefrom. What, then, is the driving force of the symptom? The power of the symptom is not the idea itself of some sexual aim, but the affect accompanying or constituting the emotional side of the idea which has become split off from the idea and has become somatized, or in other words, converted into a physical symptom. Thus the idea of castration as a punishment for a sin is split from its emotional content, the idea remains unconscious, the affect; the libido invests the eyes and we have an hysterical blindness, a symbolic castration, and it is thus with other organs or neuromuscular systems. Take for instance two common conditions, vaginismus and vomiting. The former of these disorders is a defence measure against coitus, the idea of coitus in the unconscious being coitus with the patient's father (Œdipus complex); but such an idea is abhorrent to the conscious element of the mental apparatus. It is repressed, and the affect is converted into a physical symptom which defends the patient against coitus with her husband, who is a symbol of her father. The latter (hysterical vomiting) is likewise a displacement of affect from the uterus or male sexual apparatus, the particular activity of which is forbidden and repressed; the affect is somatized or converted into a physical symptom which is symbolical of or gives vicarious expression to the forbidden activity.

This then is hysteria, a disorder that can manifest itself in almost any organ or system. The organ neurosis subserves the purpose of relieving the conscious mind of the feeling of guilt whilst giving a vicarious symbolic satisfaction to the demands of the libido.

Some would tend to simplify the psychopathology of this malady and say that a conflict between the self-preservative trends and the moral ideas of duty which give rise to great emotional stress, as, for instance, in soldiers at war, is solved by an hysterical disorder; but although such conflicts cannot be denied (they are of daily occurrence in ordinary life), yet they are but the precipitating factors, not the true causal factors, in hysteria which in common with other psychoneuroses has always a basis in the sexual life of the individual.

However, there can be no doubt that current conflicts or psychic trauma can act as ætiological factors in hysteria, but they can act in this way only if the idea of the trauma or its affect can become associated through a chain of memories, be these memories conscious or unconscious, with the unconscious memory trace of a sexual pleasure that happened in the early primitive years and which had become repressed on account of its incompatibility with the growth of "ego" ideals.

Hysteria is never the result of one ætiological factor—it has many roots, or, as Freud said, "the symptoms of hysteria are over-determined".

Diagnosis.

Hysteria has to be diagnosed from organic nervous disorder and from malingering, and at times the differentiation between these conditions may tax the ingenuity and clinical knowledge of the ablest neurologist.

It must be emphasized that hysteria may be grafted on to organic disease either as a complication or superadded syndrome to coexisting organic disease, or it may be an offspring which has continued on when the organic disorder, such as a wound, an injury to a joint *et cetera*, has passed. On the other hand hysteria may and often does combine an element of malingering—that is, of a consciously purposeful, continuation or exaggeration of symptoms.

In fact there is no sharp dividing line between hysteria and malingering; there is a gradation running from pure forms of one into pure forms of the other, pure forms of both being rare. Apart from the necessity of a careful clinical examination of the nervous system the main diagnostic technique consists in a careful history-taking of the disorder and an equally careful summing up of the character of the patient. The latter can be done only after long experience; and even as Osler said: "experience is fallacious and judgement difficult".

Treatment.

There is only one treatment for hysteria that can be relied upon as curative in the true sense and that is psychoanalysis.

But as this is impossible in many cases, we have to rely upon less laborious and less thorough methods. It is here that hypnosis is of great value. Many patients with hysterical symptoms can have the symptoms removed by suggestion under hypnosis, and for out-patient hospital practice this mode of treatment is the quickest and the easiest; in fact it may also be used as a diagnostic method, for if a symptom can be removed by hypnosis, then the patient is suffering from hysteria. That this is not universally true is shown by an experience of the writer. A returned soldier showed many curious symptoms, the chief of which were of a spastic ataxia nature; these symptoms were readily removed by hypnosis, but after a time returned and were again removed by the same method. A few weeks subsequently, however, the patient had a convulsive attack and died; a cerebral tumour was found *post mortem*.

Hypnosis is also useful in differentiating between hysteria and malingering, for it is very seldom that a patient who is malingering, even in a slight degree, will submit to hypnosis, or if he does will not respond to it; a true hysteric can always be hypnotized.

Persuasion can also be used, and is quite a successful mode of treatment in such simple hysterical symptoms as aphonia or recent contracture. Persuasion, is, however, in some cases very laborious and requires great patience. The writer once gave a whole day to the cure of an hysterical paraplegic, who at five o'clock in the afternoon was sent home walking after having been in bed for some years. It is needless to say that at the end of the treatment the doctor felt like spending a few years in bed himself.

There remains finally the treatment of those numerous cases of so-called compensation neurosis which have arisen as a result of accident insurance *et cetera*. It is almost impossible to treat these patients once the symptoms have become fixed; explanation and persuasion

sometimes are effective, but not nearly so effective as judgement of a court. Treatment in this class of disorder must be preventive; these patients must not be sent from one medical man to another, they must not become "specialized" and they must not have prolonged physical therapy.

The majority of these patients are hysterical, but the hysterical basis forms the foundation for a superstructure of malingering or semi-malingering. This latter element cannot be handled therapeutically; it must not be allowed to develop, but must be nipped in the bud by firm and judicious handling.

In spite, however, of any treatment our failures with hysterical patients will be many, and oft-times the quack succeeds where the man of much knowledge fails; after all the greatest remedy in our therapy is hope, and in the dispensing of this measure the unqualified are prodigal and well trained. Hysteria or the patient suffering from hysteria requires as little diagnosis as possible, but prompt and definite treatment. Hope must be applied in large doses—there is no room for doubt or indecision if hysteria is to be successfully treated.

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British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on May 15, 1940, at the Royal Melbourne Hospital. The meeting took the form of a number of clinical demonstrations by members of the honorary staff of the hospital.

Hodgkin's Disease.

DR. R. P. MCMEEKIN discussed the history of a female patient, aged twenty-four years, who had been admitted to hospital on June 12, 1939. A lump had been present in her left groin for two months. Six weeks prior to her admission to hospital she had had a cold, and cough with sputum had persisted since. For the last few weeks she had been growing weaker.

On examination the patient was seen to be a pale girl; her pulse rate was 70 beats per minute, her temperature was 98° F., and the systolic blood pressure was 110 and the diastolic pressure 50 millimetres of mercury. The apex beat was in the fourth left intercostal space, three inches from the mid-line. The right border of the heart could not be palpated. No abnormality was detected in the lungs. The liver and spleen were palpable. A gland the size of an almond was palpable in the left groin; it was soft, not tender, and freely movable. No other glands were palpable.

An X-ray examination on June 13 revealed no abnormality in the lungs. No tubercle bacilli were found in the sputum. A blood count gave the following information: the erythrocytes numbered 4,110,000 and the leucocytes 4,430 per cubic millimetre; the hæmoglobin value was 65% and the colour index was 0·7. On June 16 the patient's temperature was of the swinging variety, rising to 102° F. Agglutination tests gave no information, and an attempt at culture from the blood was unsuccessful. On June 26 the patient's temperature was still of the swinging type, rising to 102° F. A blood count gave the following information: the erythrocytes numbered 3,800,000 and the leucocytes 2,800 per cubic millimetre, and the hæmoglobin value was 53%; a differential leucocyte count revealed pronounced neutropenia and an obvious shift to the left.

On July 12 ascites was present, but no other glands were palpable. The erythrocytes numbered 2,740,000 and the leucocytes 2,000 per cubic millimetre; the hæmoglobin value was 45%. On July 24 the patient was very ill; gallop rhythm was present; a further blood examination revealed no change. On August 9 the liver was enlarged and tender; the patient was vomiting. On August 14 she was much better; the erythrocytes then numbered 3,590,000 and the leucocytes 2,550 per cubic millimetre, and the hæmoglobin value was 58%. On September 3 the pateint was sitting out of bed; the erythrocytes numbered 4,700,000 and the leucocytes 5,100 per cubic millimetre, and the hæmoglobin value was 88%. On September 12 the patient was discharged from hospital.

The patient was readmitted to hospital on January 2, 1940. Since her previous discharge she had been quite well until two months before her readmission, when she began to suffer from shortness of breath. For two weeks prior to her readmission to hospital she had suffered from œdema of the feet. Her temperature was 102° F. and her pulse rate 98 beats per minute. A blood count gave the following information: the erythrocytes numbered 2,600,000 and the leucocytes 2,200 per cubic millimetre; the hæmoglobin value was 44%. On January 6 the œdema was decreasing; her temperature was 101° F. and no organisms were grown on attempted culture from the blood. On January 18 she was given a blood transfusion. On January 30 the blood was still sterile; a blood count gave the following information: the erythrocytes numbered 2,500,000 and the leucocytes 2,000 per cubic millimetre; the hæmoglobin value was 46%. On February 7 a biopsy was made of the enlarged gland in the left groin; the pathologist reported that the lesion was of chronic inflammatory type, but there was no information as to its origin. On March 8 the patient was jaundiced; the liver was enlarged and tender. On March 13 death occurred.

Thrombocytopenic Purpura.

Dr. McMeekin then showed a male patient, aged forty-six years, who had been admitted to hospital on March 29, 1940. He had had petechial spots for years. He had been treated at the Children's Hospital between the ages of eight and fourteen years for recurrent epistaxis; his condition had been diagnosed as hæmophilia. Since then he had had numerous petechiæ and bruises, but had otherwise been perfectly well. One brother had had slight purpura some years earlier; two other brothers and two sisters were alive and well.

On examination the patient was found to have a temperature of 99·2° F. and a pulse rate of 112 beats per minute; his respirations numbered 24 per minute. The systolic blood pressure was 125 and the diastolic pressure 90 millimetres of mercury. No abnormality was detected in the heart or lungs; the spleen was palpable. The left ankle was enlarged and there were scattered petechiæ all over the body, with multiple bruises.

A blood count gave the following information: the hæmoglobin value was 121% and the colour index was 0·92; the erythrocytes numbered 6,560,000 and the leucocytes 6,800 per cubic millimetre; a differential leucocyte count revealed a shift to the left. The bleeding time exceeded twenty-one minutes; the blood coagulation time was within normal limits. The platelets numbered 2,130 per cubic millimetre. An X-ray examination revealed gross osteoarthritis of the left ankle, with some hypertrophic change.

Pigmentation with Splenomegaly.

Dr. McMeekin's next patient was a female, aged sixteen years, who had had pigmentation of the skin for three years; she had also suffered from languor for one year. There was nothing of note in her past or family history. The pigmentation was distributed all over her body and varied in intensity from time to time. At times the patient suffered from dyspnœa after mild exercise.

On examination she was found to have a temperature of 98·8° F.; her pulse rate was 112 beats and her respirations numbered 20 per minute; the systolic blood pressure was 130 and the diastolic pressure 80 millimetres of mercury. No abnormality was detected in the heart or lungs. The spleen was palpable; no enlarged glands were palpable. The pigmentation of the skin was dark brown in colour.

The chloride content of the blood was 573 milligrammes per 100 cubic centimetres of plasma; the fasting blood sugar level was 0·07%. No abnormal pigments were detected in the plasma. A blood count gave the following information: the hæmoglobin value was 115%; the erythrocytes numbered 5,430,000 and the leucocytes 4,750 per cubic millimetre; the colour index was 1·06. An X-ray examination revealed no abnormality in the lungs or the long bones. The urea level of the blood was 20 milligrammes *per centum*. The Wassermann test failed to elicit a reaction. The bleeding time was one minute forty seconds, and the coagulation time was fifteen minutes. Neither the Casoni nor the Mantoux test elicited a reaction. A pyelographic examination revealed that the kidneys were of normal size and outline; there was a mass anterior to the left kidney and apparently continuous with the shadow of the spleen. An X-ray examination of the skull revealed no abnormality.

(To be continued.)

Correspondence.

WAR BLINDNESS AND ITS PREVENTION.

SIR: Your leading article on the causes of war blindness is much to the point.

When conducting the man power investigation in Egypt I always had an oculist available during the sittings of the

board of which I was president, to investigate fully any doubtful ophthalmic case. In special cases they were referred to the Consulting Oculist E.E.F. for an opinion.

I am of opinion that recruits should be treated in the same way on enlistment. Whilst in the Australian Imperial Force, 1914-1916, I found some men from Australia with one eye blind and even with artificial eyes who had been passed as fit. There were many occupations in which they could be of service, but not in the first line. So long as the condition was known and noted there was nothing to complain of. But when after the war the problem of pensions was considered there was, of course, difficulty. It must be remembered that the Australian Imperial Force was not an army, but a highly efficient fighting force, and much of the supporting work was necessarily undertaken by the British Army. Britain enlisted 27% of her male population, Australia 13% and New Zealand 19%. At least two supporting men, usually more, are required for every front line man, and one-eyed men can be used in the B class, provided the condition is known and accurately noted.

Yours, etc.,

103-105, Collins Street,
Melbourne, C.1,
July 29, 1940.

JAMES W. BARRETT.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 141, of July 25, 1940.

CITIZEN NAVAL FORCES OF THE COMMONWEALTH.

Royal Australian Naval Reserve.

Promotion.—Surgeon Lieutenant Eric Leo Susman is promoted to the rank of Surgeon Lieutenant-Commander, dated 1st July, 1940.

AUSTRALIAN MILITARY FORCES.

NORTHERN COMMAND.

First Military District.

Australian Army Medical Corps.

To be Captains (provisionally) supernumerary to establishment pending absorption—Hamilton Stuart Patterson and Kenneth Stanton Crouch, 22nd June, 1940; Geoffrey Rosevear Kurrle, Kenneth Hugh Hooper and Dudley Clarence Williams, 27th June, 1940; Honorary Captains F. J. Booth, W. V. Connor, H. W. Johnson and C. C. Wark are appointed from the Reserve of Officers (A.A.M.C.), and to be Captains (provisionally) supernumerary to establishment pending absorption, 22nd June, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captains—Donald Charles Cameron Sword, 24th June, 1940; George William Mason, Beresford James Butcher, Sidney Fergus McRae Yeates, Herbert Earnshaw, Laurence Ian Burt, John George Wagner and Frederick Athol Perkins, 27th June, 1940.

EASTERN COMMAND.

Second Military District.

Australian Army Medical Corps.

To be Captains (provisionally)—John Matcham Wilshire and Michael Barry, 5th June, 1940; Leonard Reuben Israel and John Parkes Findlay and to be supernumerary to establishment pending absorption, 17th June, 1940; Walter Terence Joseph Harris, 18th June, 1940; Keith Faulkner Potts and to be supernumerary to establishment pending absorption, 18th June, 1940; Geoffrey Vernon Mutton, Edward Winchester Levings and Roderick Lionel Jeffrey, 30th June, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captains—Vivian Charles Langtree Hay, James Newell Hunton Wilson and Noel Rau, 19th June, 1940.

SOUTHERN COMMAND.

Third Military District.

Australian Army Medical Corps.

To be Captains (provisionally)—William Aitken, 20th June, 1940; John William Perry, and to be borne supernumerary to establishment pending absorption, 21st June, 1940; Charles Sullivan, Harold David Bowyer Miller, Archie Samuel Ellis, David Evans Cowenlock, and Gregory Bernard Vincent Murphy, 21st June, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captains—Reginald Henry Boyt, Loyal Alan Downes, Thomas Louis Barker, John Herbert Dorman, Arthur Montague Abey and Shirley Elliston Francis, 21st June, 1940.

Fourth Military District.

Australian Army Medical Corps Reserve.

To be Honorary Captains—Cyril Grosvenor, 30th May, 1940; Thomas Leslie McLarty and John Samuel Stewart, 12th June, 1940; John Meavious Pedler, 14th June, 1940; Graham Leslie Bennett, Laurence Claude Lum, Max Bertram Reid and John William Sangster, 17th June, 1940.

WESTERN COMMAND.

Fifth Military District.

Australian Army Medical Corps.

To be Major (temporarily)—Captain S. G. Taylor, 24th June, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captains—Theodore Godlee, 19th June, 1940; John James Savage and Norman Rose, 21st June, 1940; Ian Oriel Thorburn and Hugh Cranley Mulcahy, 26th June, 1940, and 27th June, 1940, respectively.

Research.

AN HONOUR FOR DR. W. E. L. H. CROWTHER.

AT a meeting of the Royal Society of Tasmania on July 8, 1940, His Excellency Sir Edward Clark, Governor of Tasmania, presented to Dr. W. E. L. H. Crowther, D.S.O., the medal of the Royal Society of Tasmania. In making the presentation Sir Edward Clark said that the medal, which is given at infrequent intervals, was awarded to Dr. Crowther in recognition of his prolonged anthropological research in regard to the extinct Tasmanian race and in Tasmanian history. The research was regarded as valuable to the community; Dr. Crowther had in nineteen years contributed ten papers to the *Papers and Proceedings of the Royal Society of Tasmania*, and had also published articles in other journals. We congratulate Dr. Crowther on his honour.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Practitioners Act*, 1938-1939, of New South Wales, as duly qualified medical practitioners:

Baret, Henri Victor David, M.B., B.S., 1940 (Univ. Sydney), Sydney Hospital, Sydney.

Brett, Alan Sidney, M.B., B.S., 1940 (Univ. Sydney), St. George District Hospital, Kogarah.

Burgess, John Sanday, M.B., B.S., 1940 (Univ. Sydney), 11, Bay, Road, Waverton.

Clifford, Kevin Patrick Hamilton, M.B., 1940 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.

Duncan, Ian Lovell, M.B., B.S., 1940 (Univ. Sydney), Balmain and District Hospital, Balmain.

Fletcher, Edmund Francis, M.B., B.S., 1940 (Univ. Sydney), Sydney Hospital, Sydney.

Gardiner, Ian Donald Russell, M.B., B.S., 1940 (Univ. Sydney), Royal South Sydney Hospital, Zetland.

Gillies, Douglas Neil, M.B., 1940 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.

Graham, Francis Walter, M.B., B.S., 1940 (Univ. Sydney), Manly District Hospital, Manly.

Hanrahan, Edmund Loftus Bede, M.B., B.S., 1940 (Univ. Sydney), Yandermanna, Robertson.

Humphery, Frederick Thomas, M.B., B.S., 1940 (Univ. Sydney), Lewisham Hospital, Lewisham.

Ireland, Joseph Frank, M.B., B.S., 1940 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.

Marshall, Charles Edward, M.B., 1940 (Univ. Sydney), Royal South Sydney Hospital, Zetland.

Passmore, Douglas James Buchanan, M.B., 1940 (Univ. Sydney), 81, Bonar Street, Arncliffe.

Schloeffel, Brian Ramsden, M.B., B.S., 1940 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

Shortland, Leonard Leslie, M.B., B.S., 1940 (Univ. Sydney), Western Suburbs Hospital, Croydon.

Skinner, Walter James, M.B., B.S., 1940 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.

Morgan, John Wyndham, M.B., B.S., 1911 (Univ. Melbourne), 272, Grafton Street, Woollahra.
Reye, Ralph Douglas Kenneth, M.B., B.S., 1937 (Univ. Sydney), Royal Alexandra Hospital, Camperdown.
Tulloch, Alan Keith, M.B., Ch.B., 1935 (Univ. New Zealand), F.R.C.S. (England), 1939, The Sanitarium and Hospital, Wahroonga.
McLaren, Gilbert Henry Alexander, M.B., B.S., 1937 (Univ. Melbourne), The Sanitarium and Hospital, Wahroonga.
Winton, Ronald Richmond, M.B., B.S., 1936 (Univ. Sydney), 11, Railway Street, Campbelltown.
Basto, Roberto Alexandre De Castro, M.B., B.S., 1921 (Univ. Hong-Kong), M.R.C.S. (England), L.R.C.P. (London), 1922, D.O.M.S. (R.C.P. and S., London), 1926, c.o. Bank of New South Wales, Brisbane.

The following additional qualification has been registered:

Molesworth, Edmund Harold (M.B., 1906, M.D., 1927, Univ. Sydney, F.R.A.C.P., 1939), Dip.Rad. (Univ. Sydney), 1939.

Obituary.

ARCHIBALD WATSON.

WE regret to announce the death of Professor Archibald Watson, which occurred on July 30, 1940, at Thursday Island.

THE AUSTRALIAN ARMY MEDICAL CORPS COMFORTS FUND, NEW SOUTH WALES.

IN September, 1939, the Australian Army Medical Corps Comforts Fund, New South Wales, was formed with the object of supplying comforts to all members of the Australian Army Medical Corps whilst on service in Australia or abroad.

This object has been achieved, and in the first six months £2,000 have been collected, and most of this has been expended in the supplying of actual comforts to the personnel of the Australian Army Medical Corps, both Australian Imperial Force and militia, and to medical units abroad. The administrative expenses have totalled only £40.

It is believed that the wives and friends of the officers and men of the Australian Army Medical Corps, New South Wales, both abroad and in New South Wales, might desire to become associated with the activities of this fund, and it is desired to extend to them a cordial invitation to join one of the auxiliaries.

Anyone interested in this work is asked to communicate with the President, Mrs. R. Whiston Walsh (UJ 4727), or the Honorary Secretary, Mrs. S. H. Lovell (FW 5095).

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Humphery, Frederick Thomas, M.B., B.S., 1940 (Univ. Sydney), Lewisham Hospital, Lewisham.
Shea, Leonard Thomas, M.B., B.S., 1938 (Univ. Sydney), Prince Henry Hospital, Little Bay.

Medical Appointments.

Dr. Barbara Stenhouse has been appointed Medical Officer of Health to the Bothwell Municipality, Tasmania.

* * *

Dr. A. T. Britten Jones has been appointed representative of the British Medical Association on the Dental Board of South Australia.

* * *

Dr. H. G. Cummine has been appointed Deputy Quarantine Officer at Thursday Island, pursuant to the provisions of the *Quarantine Act*, 1908-1924.

* * *

Dr. R. A. Baker has been appointed a Medical Referee for the purposes of *The Workers' Compensation Acts*, 1916 to 1939, of Queensland.

* * *

Dr. J. Coffey has been appointed Inspector of Mental Hospitals, in accordance with the provisions of *The Public Service Acts*, 1922 to 1924, and *The Mental Hygiene Act of* 1938, of Queensland.

Diary for the Month.

AUG. 13.—Tasmanian Branch, B.M.A.: Branch.
AUG. 13.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
AUG. 20.—New South Wales Branch, B.M.A.: Ethics Committee.
AUG. 21.—Western Australian Branch, B.M.A.: Branch.
AUG. 22.—New South Wales Branch, B.M.A.: Clinical meeting.
AUG. 23.—Queensland Branch, B.M.A.: Council.
AUG. 27.—New South Wales Branch, B.M.A.: Medical Politics Committee.
AUG. 28.—Victorian Branch, B.M.A.: Council.
AUG. 29.—New South Wales Branch, B.M.A.: Branch.
AUG. 29.—South Australian Branch, B.M.A.: Branch.
AUG. 30.—Tasmanian Branch, B.M.A.: Council.
SEPT. 3.—New South Wales Branch, B.M.A.: Organization and Science Committee.
SEPT. 3.—Federal Council, B.M.A.: Meeting at Sydney.
SEPT. 4.—Victorian Branch, B.M.A.: Branch.
SEPT. 4.—Western Australian Branch, B.M.A.: Council.
SEPT. 5.—South Australian Branch, B.M.A.: Council.
SEPT. 6.—Queensland Branch, B.M.A.: Branch (Jackson Lecture).
SEPT. 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
SEPT. 10.—Tasmanian Branch, B.M.A.: Branch.
SEPT. 13.—Queensland Branch, B.M.A.: Council.
SEPT. 17.—New South Wales Branch, B.M.A.: Ethics Committee.
SEPT. 18.—Western Australian Branch, B.M.A.: Branch.
SEPT. 19.—New South Wales Branch, B.M.A.: Clinical Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associate Friendly Societies' Medical Institute; Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

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